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[Prevention Treatment Rehabilitation]

Dear Colleagues:

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Contents

Editorial

Dear Colleagues,

You are holding in your hand the first edition of our journal "Archiv EuroMedica", which was published by the Editorial Board of European Scientific Society in Hanover. Among the authors there are specialists from various fields of medicine representing 15 countries: Germany, USA, Russia, Ukraine, China, Bulgaria, Azerbaijan, Kazakhstan, Great Britain, Armenia, Sweden, Japan, Poland, Australia, and Switzerland.

The 20th century has dramatically changed medicine and health care system all over the world. Today it is a powerful industry comprising plenty of networks: treatment and prevention facilities, scientific institutions, medical universities and a strong pharmaceutical branch.

We have been watching a radical industrialization of medicine – rapid introduction of latest technologies into medicine and its splitting into numerous disciplines and directions, whose number is constantly growing. It is obvious, that the volume of information that a doctor has to command has been greatly increased. It is also clear that to grasp this variety of novelties is getting every year harder and harder. Only participation in seminars, conferences and reading of special medical literature enables to solve this problem.

Congresses „Euromedica" that are held annually in Hanover since 2006 are becoming a tradition. A major target put forward by European Scientific Society is scientific exchange between scientists and specialists from different fields of medicine.

We hope that the journal "Archiv EuroMedica" is going to become one more chain that unites doctors from different countries and one more step in improving the quality of medical performance.

Sincerely,

Your Editorial Board: Georgy Tyminskiy

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Editorial Board

Progressive necrotizing enterocolitis of newborns. Validity of step-by-step treatment of the complicated forms

Michail Akselrov, Alexander Stolyar

The stress and centralization of a circulation at the newborn can conduct to local disturbance mesenteric blood flow, to disturbance of barrier function of a mucous intestinal tube, a translocation of microbes in a vascular bed, to an ulceration mucous, to a coagulative necrosis, perforations. Occurrence of destructive changes from an intestine, needs inevitably operative treatment. Surgeons are use: suture ligation of perforations, a bowel resection with anastomosis, formation of time intestinal ostomies in various variants. In spite of big spectrum of the offered operative measures, results of treatment it is frequent not satisfactory, the lethality reaches 30-40 %, and at an extensive lesion of 80-100 % [1-6,8,9].

Under our observation (Regional hospital No 2 Tyumen, Russia), during 1988 on 2009r, were 74 patients (boys - 47; girls - 27) with progressing necrotic coloenteritis III a-b stages (classification Walsh, Kliegman). All children in pre-natal development, in the course of a birth or days of life were submitted for the first time to influence of the various factors which have caused a hypoxia. Middle age of mothers 25,5±5,1 (21; 25; 30) years. In the anamnesis abortions have of 54,1 % of parturient women. The pre-natal becoming infected is established in 48,7 % observations, 91,2 % of mothers have transferred to pregnancy time infectious-inflammatory or somatopathies, 78,4% suffered serious gestosis, at 100 % took place a chronic placental insufficiency. 82,4% of children were prematurely born. The average gestational age was 33,2±4,4 (29,33,36) weeks. The average mass of a body of children at a birth was 2070±871 (1309,1885, 2627) gram. In our clinic step-by-step approach to treatment applied since 2000.

Perforations in an intestine arose during the period from 7 till 21 days, on 13,7±11,1 (5; 10; 19) day after a birth. All patients arrived in extremely grave condition caused by peritoneal shock, compartment syndrome, a sepsis expressed by water-electrolytic disturbances, IDCS implications, at 46 % purulent complications, and at 47,3 % accompanying developmental anomalies. Laparocentesis helps to lower intraabdominal pressure. At patients with a pneumoperitoneum, intraabdominal pressure at entering is peer (I. Kron and coworkers. [7]) 24,65±3,29 mm Hg. (norm 4,35±1,76 mm Hg). The abdominal cavity drainage reduces level of intrabdominal pressure in 1,5 times (P <0,001) that considerably facilitates excursion of lungs and allows to optimize preoperative preparation. All patients are operated. Ulcer-necrotic process is taped only in a small bowel at 63,5 %, only in thick at 23 %, both in thin, and in a colon at 13,5 % of patients. Plural perforations are found out at 49 (66,2 %), individual - at 25 (33,8 %) patients. At all newborns the operative measure came to an end with formation of a time artificial intestinal fistula. Deducing of an intestinal ostomy conducted to leukocytosis depression, reduction of inflammatory shift and reduction of level of an endogenous intoxication. For days the leukocytic index of an intoxication decreased with 4,7±5,4 to 3,3±4, and by 7 days came to norm 0,6±0,6 (P <0,05). At 65 patients deduced terminal enteral- or colostoma. A technique rather simplicity. Complexities arise in the postoperative period and are bound to necessity of indemnification of the big losses of a chyme massive intravenous injections. Facilitates postoperative conducting children injection in a distal ostomy of water and nutritious admixtures. The anastomosis has been generated at 14,9 % of patients on a principle «the extremity sideways» or «a side sideways» with deducing on a forward abdominal wall of a resulting or taking away loop of an intestine. At extremely grave condition, for putting off of an intraabdominal hypertensia and peritonitis treatment, at 9 (12,2 %) newborns, entero- and (or) colostoma we supplemented deducing laparostoma by the technique accepted in clinic (open conducting an abdominal cavity). In the postoperative period all children at first full received the parenteral food, then partial with gradual transition, at occurrence of a peristalsis of an intestine on the enteral. Closing of an intestinal fistula spent after normalization of the relation of aerobic microorganisms of an intestine to anaerobic, applying standard schemes of treatment both scarce, and a pathogenic dysbacteriosis. Application described stap-by-step treatment has allowed to lower quantity of complications with 40 to 18,5 % (hi-kvadrat=2,585; P=0,108), and a lethality from 65 % to 42,6 % (hi-kvadrat=2,105; P=0,147).

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Phases and perspectives of complementary therapies in rehabilitation

Marina Askamakina[1], Semen Golosheikin[2]

Method of self-healing, self-regulation, self-knowledge was discovered by Mrs. Nirmala Srivastava (Shri Mataji Nirmala Devi) on 5th of May, 1970.

Mrs. Nirmala Srivastava was born at noon on March 21, 1923, during the spring equinox, in Chindawara, Central part of India, in a noble Christian family. In her childhood Nirmala was in the ashram of Mahatma Gandhi, who discovered her extraordinary gifts, and often asked her for suggestions. After graduating from high school, and being a student at Medical College, Shri Mataji took active part in India's Liberation Movement for independence.

In 1947 Shri Mataji married a exceptional person, Sir C.P.Srivastava, who was elected for 16 consecutive years to be the Secretary General of the United Nations International Maritime Organization. They have two married daughters and four grandchildren.

Through experimental work in the beginning of the 70s, Shri Mataji created her own system, called as Sahaja Yoga. Thanks to it, it became possible to awaken the subtle Kundalini energy en-mass in hundreds and thousands of people at the same time.

Shri Mataji has received a UN award of World Peace in recognition of Her work for global peace. She is recognized as an honored citizen of many cities worldwide. In 1997 She was named Personality of the globe by the United Earth Organization. Nowadays Sahaja Yoga centers are established in more than hundred countries all over the planet.

In Russia this unique method Sahaja Yoga exists and gets developed since 1989, and in Novosibirsk since 1990. Applying Sahaja Yoga methods in Medicine has shown their huge efficiency. In 2004 to The Autonomic Nonprofit Organization "Sahaja Yoga" was granted a Diploma of participation in the competition "Best diagnostics and healing technology of recovering medicine – 2003". It was included in the program "protection and health strengthening of healthy people in 2003-2010".

Simple methods of bringing of the nervous system into balance and recovering of self energy centers are created in Sahaja Yoga. As a result, all built-in within human being principles get awakened, and the functioning of the whole body gets to normal. Meditation is the major work in Sahaja Yoga. One stays in full consciousness during meditation, which leads to relaxation of the brain, and of the nervous system, and activates the inner energy. Even though the process of awakening of the inner energy takes 10-15 min, human body gets balanced fast.

Dr. Marina Askamakina
medical therapist, high category

Phases of applying Sahaja Yoga in medicine:

This methodology is used for healing of patients since 1992 in Novosibirsk. Since 1995 up to now regular self-regulatory Sahaja Yoga sessions take place on Saturdays in Municipal polyclinic of 21.

First Phase of our application was monitoring of surgical and therapeutic diseases in patients in 7 hospitals and 7 polyclinics in the city. First phase ended with positive effect on the individuals.

During the Second Phase we decided to check the financial effect of Sahaja Yoga in medicine.

For this purpose we did monitor patients in a period of time when epidemic flue was taking place. We encountered the duration off work of patients, suffering different diseases. Time off work decreased noticeably among patients with respiratory infection and tracheo-bronchitis. Tendency

[1]*municipal polyclinic of 21, Russia, Novosibirsk*
[2]*Saint Louise, USA*

occurred in decreasing the stay at hospital for the patients with arterial hypertension, and hip-osteoporosis (Appendix 1).
Third Phase of our scientific experiment during year 2000-2001 was to figure out the most frequently impacted energy centers in different illnesses.
Among 100 patients with 7 different diseases we figured out that the second center swadistan gets affected within all patients.
We also noticed that patients with artery hypertension and chronicle pancreatitis get a problem of their swadistan, and anahata centers. We discovered that patients with the same disease had a variety of imbalance-combinations of their energy centers.
Another significant finding in our experiment was the relation between socially important risk-factors of the diseases (gender, marital status, education, and job) and the malfunctioning energy centers.
At this time we would like to stress on the fact that after the second diagnostic check-up of the patients, regardless of the improvement of their physical condition, problems in the imbalanced energy centers continued existing.
In year 2002 an opportunity occurred to hold a common experiment with The Scientific Therapeutic Institute of Russian Academy of Sciences in the city of Novosibirsk (led by the candidate of medical sciences Girgolkau L.A.). Comparison diagnostics of the subtle system took place among the population of Novosibirsk and Chukotka. Results demonstrated the same pattern as in the previous experiments. All patients who were using methodology of Sahaja Yoga, recovered faster, and they showed a remission of chronicle diseases, and a soft process of obstructions (Appendix 2, 3).
In April 2006 a Health Center was established for patients with asthma in Municipal Polyclinic 21, which was visited by patients with other sicknesses. Since 2007 a complex health-recovery methodology started being practiced in Municipal Polyclinic 21 (Appendix 4).
Since 2008 a Training Center started functioning for the patients with artery hypertension. One of the sessions is completely dedicated to coping with stress from Sahaja Yoga point of view.
Patients started being invited to meditation sessions on Saturdays in Municipal Polyclinic 21 (Appendix 5).
In this approach, step by step, we started using Sahaja Yoga in medicine – Cabinet of Psycho- physiological self-regulation (CPS). Its methodology was kindly offered to the doctors, for further application, by the Candidate of Biological Sciences Semen Alexandrovich Golosheikin, neurophysiologist in Saint Louise, USA.
In the CPS Project there is a scientific explanation of the Cabinet, General conditions, major duties of CPS, major methods and functions of CPS, list of offered services, general suggestions and precautions in practicing of CPS course.
Major duty of CPS is creation, upgrading of application methods, and optimization of technologies in functioning of regulation systems on behavioral and somatic stages of healthy people, and of patients with psychosomatic diseases.
Major principles of CPS are:
1. Program selection of the sessions to be individually based on the symptoms
2. Minimal number of the sessions is 7
3. Duration of one session is 1,5 – 2 hours
4. Sessions are hold no earlier than 60 min after eating food, but not on empty stomach
5.Sessions take place only in case if one has not used:
Alcohol for the last 48 hours
Coffee, strong tea, caffeine containing products during the last 2 hours
Smoking – the last 1 hour
In the current moment Polyclinic cannot use Sahaja Yoga the same way as CPS because of lack of available cabinet. Training self-regulation center and Training center for patients with artery hypertension take place in the doctor's cabinets out of their regular working day hours.
Capacity and will to work are out there.

Pica associated with iron deficiency or depletion: clinical and laboratory correlates in 262 non-pregnant adult outpatients

James C Barton[1,2,3], J Clayborn Barton[1] and Luigi F Bertoli[1,3,4]

Abstract

Background

There are many descriptions of the association of pica with iron deficiency in adults, but there are few reports in which observations available at diagnosis of iron deficiency were analyzed using multivariable techniques to identify significant predictors of pica. We sought to identify clinical

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and laboratory correlates of pica in adults with iron deficiency or depletion using univariable and stepwise forward logistic regression analyses.

Methods

We reviewed charts of 262 non-pregnant adult outpatients (ages ≥18 y) who required treatment with intravenous iron dextran. We tabulated their sex, age, race/ethnicity, body mass index, symptoms and causes of iron deficiency or depletion, serum iron and complete blood count measures, and other conditions at diagnosis before intravenous iron dextran was administered. We excluded patients with serum creatinine >133 μmol/L or disorders that could affect erythrocyte or iron measures. Iron deficiency was defined as both SF <45 pmol/L and TS <10%. Iron depletion was defined as serum ferritin (SF) <112 pmol/L. We performed univariable comparisons and stepwise forward logistic regression analyses to identify significant correlates of pica.

Results

There were 230 women (184 white, 46 black; ages 19-91 y) and 32 men (31 white, 1 black; ages 24-81 y). 118 patients (45.0%) reported pica; of these, 87.3% reported ice pica (pagophagia). In univariable analyses, patients with pica had lower mean age, black race/ethnicity, and higher prevalences of cardiopulmonary and epithelial manifestations. The prevalence of iron deficiency, with or without anemia, did not differ significantly between patients with and without pica reports. Mean hemoglobin and mean corpuscular volume (MCV) were lower and mean red blood cell distribution width (RDW) and platelet count were higher in patients with pica. Thrombocytosis occurred only in women and was more prevalent in those with pica (20.4% vs. 8.3%; p = 0.0050). Mean total iron-binding capacity was higher and mean serum ferritin was lower in patients with pica. Nineteen patients developed a second episode of iron deficiency or depletion; concordance of recurrent pica (or absence of pica) was 95%. Predictors of pica in logistic regression analyses were age and MCV (negative associations; p = 0.0250 and 0.0018, respectively) and RDW and platelet count (positive associations; p = 0.0009 and 0.02215, respectively); the odds ratios of these predictors were low.

Conclusions

In non-pregnant adult patients with iron deficiency or depletion, lower age is a significant predictor of pica. Patients with pica have lower MCV, higher RDW, and higher platelet counts than patients without pica.

Background

Pica is the daily compulsive eating of food or non-food items not part of one's habitual diet or preferences. Pica is a distinctive but poorly understood accompaniment of iron deficiency or depletion in some adults, although most pica items contain little or no iron. Hippocrates wrote that "a craving to eat earth" was associated with "corruption of the blood" [1,2]. In the early 15th C, de Cervantes reported a history in which "women that by caprice eat soil, plaster, coal and other disgusting substances" [3]. Physicians of the 19th C reported that persons with chlorosis (predominantly women) had "various forms of pica or morbid appetite, as for pickles, magnesia, cinders, &c" [4], or "capricious appetite" [5]. Individual adults with pica associated with iron deficiency or depletion typically ingest only one or a few substances in a compulsive manner. Pica items are diverse, and vary according to race/ethnicity, culture, and geographic location [1,6-10].

Many reports describe substances that patients with iron deficiency consumed in a compulsive manner, and effects of treatment of iron deficiency on pica [1,4,6-12]. There are few reports in which observations available at diagnosis of iron deficiency were evaluated using multivariable analyses to identify possible significant differences between persons who did and did not develop pica. In a case-control study from France, a logistic regression model demonstrated that iron deficiency and being non-European were significant independent predictors of pica [9]. Significant race/ethnicity differences in the prevalence of pica have also been reported in other iron deficiency case series [8,11,13-15]. Among iron-deficient adults of the same race/ethnicity, some develop pica and others do not [8,11,13-15]. These observations suggest that heritable traits could contribute to pica susceptibility in adults with iron deficiency. It is generally accepted that some patients who developed pica with an initial episode of iron deficiency will develop pica during subsequent episodes of iron deficiency [13,16,17]. Regardless, we were unable to identify reports in which the concordance of pica or no pica with successive episodes of iron deficiency in the same series of patients was quantified. High concordance also suggests that heritable factors increase the likelihood that pica would accompany iron deficiency.

We sought to identify clinical and laboratory correlates of pica in 262 consecutive non-pregnant adult outpatients at diagnosis of iron deficiency or depletion. These patients were referred because they needed treatment with intravenous iron. In each case, we tabulated sex, age, race/ethnicity, body mass index, symptoms attributed to iron deficiency or depletion, causes of iron deficiency or depletion, serum iron and complete blood count (CBC) measures, and other medical conditions at diagnosis of iron deficiency before intravenous iron was administered. We performed univariable and multivariable analyses to identify significant positive and negative predictors of pica. We compared and contrasted our results with previous reports of pica associated with iron deficiency, and discuss abnormalities that could account for pica in iron deficiency and depletion.

Methods

Patient selection

The performance of this study was approved by the Institutional Review Board of Brookwood Medical Center. We performed retrospective reviews of the charts of all adult outpatients (≥18 years of age) who were treated with intravenous iron dextran in a single referral hematology and medical oncology practice during the interval 2002-2009. Cases were identified by computerized and manual searches of practice medical and billing records for International Classification of Diseases (ICD) code 280.0 (iron deficiency), ICD code 307.52 (pica), and procedure codes corresponding to administration of intravenous iron dextran. Each patient was evaluated by either JCB or LFB. Each patient was treated with intravenous iron dextran (Imferon® or INFed®; Watson Pharma, Inc., Morristown, NJ) because he/she could not tolerate oral iron supplements; his/her iron deficiency or depletion did not resolve with trials of oral iron supplementation; or he/she had anemia or other manifestation(s) too severe to manage with oral iron supplements [8].

We excluded patients who were pregnant; were hospitalized; had serum creatinine >133 μmol/L; had been treated with

erythrocyte transfusion to alleviate anemia; had types of acquired anemia other than that due to iron deficiency or depletion; had erythrocytosis, polycythemia, or other bone marrow disorder not in remission; were receiving anti-cancer chemotherapy or radiation therapy; or had hyperferritinemia due to acute phase reaction, chronic inflammation, liver injury, malignancy, or other cause.

Laboratory techniques

CBCs were performed using Cell-Dyn® 1800 or 1500 automated blood counters (Abbott Laboratories, Chicago, IL). Reference ranges for red blood cells (RBC), mean corpuscular volume (MCV), and red blood cell distribution width (RDW) are 4.20-6.30 × 1012/L, 80.0-97.0 fL, and 11.5-14.5%, respectively. Anemia was defined as hemoglobin below these lower reference limits (133 g/L, men; 117 g/L, women) [18]. Thrombocytopenia was defined as platelet count <140 × 109/L; thrombocytosis was defined as platelet count >440 × 109/L. Serum iron measures were determined using automated clinical laboratory methods. Total iron-binding capacity (TIBC) was defined as the sum of serum iron (SI) concentration and unbound iron-binding capacity. Transferrin saturation (TS) was defined as the quotient of serum iron concentration by TIBC. Iron deficiency was defined as both serum ferritin (SF) <45 pmol/L and TS <10%. Iron depletion was defined as SF <112 pmol/L.

Definition of pica

Pica was defined as the daily compulsive eating of food or non-food items, singly or in combination, not ordinarily part of the patient's habitual diet or preferences, for more than one month, and not reasonably attributable to causes other than iron deficiency by the patient or treating physician. We tabulated pica food and non-food items in each case. Most patients were questioned specifically at the time of their initial evaluation for iron deficiency about whether they had pica. Patients whose charts had no report of pica were classified as not having pica.

Observations for tabulation

We compiled these observations at diagnosis in all eligible patients: age, sex, self-reported race/ethnicity, body mass index (BMI), and presence (or absence) of pica reports. We also recorded and categorized symptoms attributed to iron deficiency or depletion, defined as fatigue (fatigue, weakness, decreased stamina); cardiopulmonary symptoms (shortness of breath, dyspnea on exertion, palpitations, dizziness, syncope); mental manifestations (forgetfulness, slow mentation; difficulty in performing routine mental tasks); epithelial manifestations (angular, cheilosis, glossitis, stomatitis, dysphagia, esophageal web, hair or nail changes, easy bruising); and neuromuscular symptoms (restless legs syndrome (RLS) [19], involuntary muscle contractions, paresthesias).

We grouped causes of iron deficiency or depletion according to these categories: 1) gastrointestinal blood loss, regardless of lesion(s); 2) reproductive tract loss (menses and previous pregnancy); 3) medical losses (laboratory testing, voluntary blood donation, therapeutic phlebotomy, or surgery); 4) chronic malabsorption (gastric bypass surgery, celiac disease, gastric resection); 5) urinary tract blood loss (hematuria); 6) recurrent epistaxis; and 7) unknown cause. One or two predominant causes were recorded in each case according to interpretation of the treating physician and our chart review.

We recorded the presence or absence of some other conditions in each subject because these conditions are common among patients in our practice: cancer in remission (any malignancy other than non-melanoma skin cancer); common variable immunodeficiency (CVID); diabetes mellitus; and HFE hemochromatosis associated with C282Y homozygosity. We compiled values of hemoglobin, RBC, MCV, and RDW; lymphocyte, neutrophil, and platelet counts; and SI, TIBC, TS, and SF levels at diagnosis before intravenous iron dextran therapy was administered.

Pica and recurrent iron depletion or deficiency

In this substudy, we tabulated the presence or absence of pica detected in patients with recurrent iron deficiency or depletion more than six months after resolution of clinical and laboratory abnormalities associated with their respective initial episodes of iron deficiency or depletion.

Statistical considerations

We reviewed the charts of 267 patients; five cases were excluded because the chart did not contain all variables specified for the present analyses. Thus, the analytic dataset included observations on 262 patients. Continuous variables included age at diagnosis, BMI, CBC values, and serum iron measures. Dichotomous variables included sex, race/ethnicity (white vs. black/African American), presence or absence of pica and other symptoms or conditions attributed to iron deficiency or depletion, causes of iron deficiency or depletion, and history or no history of cancer in remission, CVID, diabetes mellitus, and hemochromatosis. Altogether, there were 32 variables (pica and 31 others). TIBC values >86.8 µmol/L were imputed as 87.0 µmol/L; SF values reported as <4.5 pmol/L were imputed as 2.2 pmol/L. We analyzed the categories anemia, iron deficiency, iron depletion, thrombocytosis, thrombocytopenia, and anemia and iron deficiency in univariable but not multivariable analyses, because each of these categories is derived from measured values. Observations analyzed on 18 persons who had recurrent iron depletion or deficiency included recurrence of pica, CBC values, and serum iron measures.

Descriptive statistics are displayed as enumerations, percentages, frequency distribution plots, or mean ± 1 standard deviation (SD). Comparisons were made using either Student's two-sided t-test or chi-square or Fisher's exact test, as appropriate. We performed stepwise forward multiple logistic regression analyses to identify independent factors that have a significant positive or negative association with pica (dependent variable). Results of the final model are expressed as beta coefficient, standard error (SE), Wald coefficient/SE, probability, and odds ratios (95% confidence interval (CI)). Data analyses were performed using GB-Stat® v 8.0 (Dynamic Microsystems, Inc., Silver Spring, MD) and Microsoft Excel 2000® (Microsoft Corp., Redmond, WA). Values of $p < 0.05$ are defined as significant.

Results

General characteristics of study subjects

All patients were treated with intravenous iron dextran in the interval November 1992-March 2009. There were 230 women (184 white, 46 black) and 32 men (31 white, 1 black). The age range of women was 19-91 years; the age range of men was 24-81 years (Table 1).

There were reports of pica in 118 patients (45.0%) (Table 1), and chart documentation of no pica in 49 other cases. Thus,

Table 1. Characteristics of 262 adults with iron deficiency or depletion[1]

Characteristic	White women (184)	White men (31)	Black women (46)	Black men (1)
Age, y	54 ± 16	62 ± 16	42 ± 15	58
Body mass index, kg/m^2	28.9 ± 7.6	29.0 ± 6.3	32.0 ± 9.4	29.6
Pica, % (n)	42.9 (79)	32.3 (10)	63.0 (29)	0
Fatigue, % (n)	41.3 (76)	41.9 (13)	54.3 (25)	100.0 (1)
Cardiopulmonary symptoms, % (n)	28.8 (53)	38.7 (12)	60.9 (28)	0
Epithelial manifestations, % (n)	26.1 (48)	16.1 (5)	19.6 (9)	0
Mental manifestations, % (n)	6.0 (11)	6.5 (2)	0	0
Neuromuscular symptoms, % (n)	4.9 (9)	6.5 (2)	6.5 (3)	0
Gastrointestinal blood loss, % (n)	42.4 (78)	77.4 (24)	17.4 (8)	100.0 (1)
Reproductive blood loss, % (n)	30.4 (56)	-	60.9 (28)	-
Medical blood loss, % (n)	14.1 (26)	9.7 (3)	4.4 (2)	0
Hematuria, % (n)	1.6 (3)	0	0	0
Epistaxis, % (n)	0	6.5 (2)	0	0
Chronic malabsorption, % (n)	12.0 (22)	3.2 (1)	13.0 (6)	0
Unknown cause of iron deficiency/depletion, % (n)	6.5 (12)	9.7 (3)	8.7 (4)	0
Hemoglobin, g/L	106 ± 19	105 ± 25	93 ± 20	13.6
MCV, fL	79.5 ± 9.9	78.6 ± 8.2	72.5 ± 16.2	81.0
RBC × 10^{12}/L	4.14 ± 0.63	4.16 ± 0.81	3.93 ± 0.69	5.45
RDW, %	17.3 ± 2.8	18.7 ± 3.5	19.3 ± 4.4	16.8
Platelets × 10^9/L	327 ± 135	264 ± 84	367 ± 125	199
Lymphocytes × 10^9/L	2.0 ± 0.9	1.8 ± 0.9	2.0 ± 0.9	3.7
Neutrophils × 10^9/L	4.5 ± 2.2	4.4 ± 2.0	3.6 ± 1.5	3.4
SI, µmol/L	7 ± 5	7 ± 4	8 ± 6	9
TIBC, µmol/L	74 ± 13	70 ± 14	71 ± 14	60
TS, %	10 ± 7	11 ± 8	10 ± 6	15
SF, pmol/L	29 ± 25	36 ± 25	27 ± 22	58
Cancer in remission, % (n)	11.4 (21)	22.6 (7)	13.0 (6)	100.0 (1)
CVID, % (n)	21.2 (39)	0	0	0
Diabetes mellitus, % (n)	15.2 (28)	19.4 (6)	13.0 (6)	0
Hemochromatosis, % (n)	2.7 (5)	0	0	0
Anemia, % (n)	46.2 (85)	90.3 (28)	93.5 (43)	0
Thrombocytosis, % (n)	14.1 (26)	0	21.7 (10)	0
Thrombocytopenia, % (n)	3.8 (7)	9.7 (3)	0	0
Iron deficiency, % (n)	63.6 (117)	48.4 (15)	69.6 (32)	0
Iron deficiency and anemia, % (n)	46.7 (86)	35.5 (11)	63.0 (29)	0

1Results are expressed as mean ± 1 SD or as percentage (n). Abbreviations: MCV, mean corpuscular volume; RBC, red blood cells; RDW, red blood cell distribution width; SI, serum iron; TIBC, total iron-binding capacity; TS, transferrin saturation; SF, serum ferritin; CVID, common variable immunodeficiency.

there were explicit reports of pica or no pica in 63.7% of all 262 cases. Among all 262 subjects, the proportion of women with pica did not differ significantly from the proportion of men with pica (47.0% vs. 31.3%, respectively; p = 0.0943). The proportion of whites with reports of pica was lower than the proportion of blacks with pica (41.1% vs. 61.7%, respectively; p = 0.0113). Among women, the proportion of whites with reports of pica was lower than the proportion of blacks with pica (42.9% vs. 63.0%, respectively; p = 0.0145).

Fatigue, cardiopulmonary symptoms, and epithelial manifestations were common among all 262 subjects (43.9%, 35.5%, and 23.7%, respectively). Gastrointestinal blood loss occurred in 42.4% and medical blood loss in 11.8% of all subjects; 36.5% of women had reproductive tract blood loss. Chronic malabsorption occurred in 29 patients (11.2%), 28 of whom (96.6%) were women. Diagnoses of CVID and

Table 2. Comparisons of 103 adults with pagophagia and 15 adults with non-ice pica[1]

Characteristic	Report of pagophagia (n = 103) [2]	Pica without report of ice (n = 15)	Value of p [3]
Age, y	49 ± 15	52 ± 18	0.5056
Women, % (n)	90.3 (93)	100.0 (15)	0.2421
White, % (n)	74.8 (77)	80.0 (12)	0.4693
Body mass index, kg/m^2	29.7 ± 7.6	30.1 ± 11.2	0.8857
Fatigue, % (n)	45.6 (47)	53.3 (8)	0.5764
Cardiopulmonary symptoms, % (n)	42.7 (44)	46.7 (7)	0.7730
Epithelial manifestations, % (n)	26.2 (27)	53.3 (8)	0.0361
Mental symptoms, % (n)	6.8 (7)	0 (0)	0.3758
Neuromuscular symptoms, % (n)	6.8 (7)	0 (0)	0.3758
Gastrointestinal blood loss, % (n)	36.9 (38)	33.3 (5)	0.7890
Reproductive blood loss, % (n)	43.7 (45)	20.0 (3)	0.0684
Epistaxis, % (n)	0 (0)	0 (0)	-
Hematuria, % (n)	1.0 (1)	0 (0)	0.8729
Medical blood loss, % (n)	5.8 (6)	20.0 (3)	0.0877
Chronic malabsorption, % (n)	8.7 (9)	40.0 (6)	0.0007
Unknown cause of iron deficiency/depletion, % (n)	8.7 (9)	6.7 (1)	0.7879
Hemoglobin, g/L	99 ± 21	110 ± 26	0.2471
MCV, fL	73.8 ± 13.1	82.7 ± 8.9	0.0026
RBC × 10^{12}/L	4.16 ± 0.58	4.11 ± 0.95	0.8764
RDW, %	18.7 ± 3.9	17.7 ± 2.3	0.1637
Platelets × 10^9/L	336 ± 118	464 ± 247	0.0669
Lymphocytes × 10^9/L	1.8 ± 0.8	2.2 ± 0.7	0.1012
Neutrophils × 10^9/L	4.2 ± 2.1	4.8 ± 2.0	0.3587
SI, µmol/L	7 ± 5	7 ± 4	0.8412
TIBC, µmol/L	75 ± 13	77 ± 3	0.5761
TS, %	9 ± 8	9 ± 6	0.8805
SF, pmol/L	27 ± 22	27 ± 5	0.8883
Cancer in remission, %	8.7 (9)	0 (0)	0.2807
CVID, %	9.7 (10)	20.0 (3)	0.2154
Diabetes mellitus, %	13.6 (14)	0 (0)	0.1319
Hemochromatosis, %	1.0 (1)	0 (0)	0.8729
Anemia, % (n)	81.6 (84)	66.7 (10)	0.1808
Thrombocytosis, % (n)	16.5 (17)	46.7 (7)	0.0067
Thrombocytopenia, % (n)	2.9 (3)	6.7 (1)	0.4432
Iron deficiency, % (n)	68.0 (70)	66.7 (10)	0.9201
Iron deficiency with anemia, % (n)	55.3 (57)	40.0 (6)	0.2658

1Results are expressed as mean ± 1 SD or as percentage (n). Abbreviations: MCV, mean corpuscular volume; RBC, red blood cells; RDW, red blood cell distribution width; SI, serum iron; TIBC, total iron-binding capacity; TS, transferrin saturation; SF, serum ferritin; CVID, common variable immunodeficiency.

2Each of these patients reported pica for ice (pagophagia); some patients reported two or more pica items.

3Comparisons were made using Student's two-tailed t-test, Chi-square test, or Fisher's exact test, as appropriate.

hemochromatosis were observed only in white women. Thrombocytosis occurred only in women (n = 36; 15.6%) (Table 1).

Univariable comparisons of subjects with ice pica (pagophagia) and non-ice pica

Epithelial manifestations and chronic malabsorption were less prevalent in 103 patients with pagophagia than in 15 patients with non-ice pica (Table 2). Mean MCV and the prevalence of thrombocytosis were lower in patients

Table 3. Comparisons of 118 adults with pica and 144 adults without pica1

Characteristic	Report of pica (n = 118) 2	No report of pica (n = 144)	Value of p 3
Age, y	50 ± 15	55 ± 17	0.0041
Women, % (n)	91.5 (108)	84.7 (122)	0.0943
White, % (n)	75.4 (89)	87.5 (126)	0.0113
Body mass index, kg/m2	29.7 ± 8.1	29.3 ± 7.7	0.6667
Fatigue, % (n)	46.6 (55)	41.7 (60)	0.4224
Cardiopulmonary symptoms, % (n)	43.2 (51)	29.2 (42)	0.0180
Epithelial manifestations, % (n)	29.7 (35)	18.8 (7)	0.0387
Mental symptoms, % (n)	5.9 (7)	4.2 (6)	0.5126
Neuromuscular symptoms, % (n)	5.9 (7)	4.9 (7)	0.7013
Gastrointestinal blood loss, % (n)	36.4 (43)	47.2 (68)	0.2411
Reproductive blood loss, % (n)	40.7 (48)	25.0 (36)	0.0068
Epistaxis, % (n)	0	1.4 (2)	0.3011
Hematuria, % (n)	0.8 (1)	1.4 (2)	0.5745
Medical blood loss, % (n)	7.6 (9)	15.3 (22)	0.0564
Chronic malabsorption, % (n)	12.7 (15)	9.7 (14)	0.4429
Unknown cause of iron deficiency/depletion, % (n)	8.5 (10)	6.3 (9)	0.4897
Hemoglobin, g/L	100 ± 22	107 ± 22	0.0251
MCV, fL	75.0 ± 13.0	80.8 ± 9.0	0.0001
RBC × 1012/L	4.15 ± 0.64	4.08 ± 0.70	0.4232
RDW, %	18.6 ± 3.7	17.2 ± 2.7	0.0006
Platelets × 109/L	352 ± 146	305 ± 113	0.0046
Lymphocytes × 109/L	1.9 ± 0.7	2.0 ± 1.0	0.4120
Neutrophils × 109/L	4.3 ± 2.1	4.3 ± 2.1	0.9327
SI, µmol/L	7 ± 5	8 ± 5	0.1304
TIBC, µmol/L	75 ± 13	72 ± 14	0.0476
TS, %	10 ± 7	11 ± 7	0.1124
SF, pmol/L	27 ± 22	34 ± 25	0.0248
Cancer in remission, %	7.6 (9)	18.1 (26)	0.0136
CVID, %	11.0 (13)	18.1 (26)	0.1113
Diabetes mellitus, %	11.9 (14)	18.1 (26)	0.1657
Hemochromatosis, %	0.8 (1)	2.8 (4)	0.2533
Anemia, % (n)	79.7 (94)	69.4 (100)	0.0605
Thrombocytosis, % (n)	20.4 (24)	8.3 (12)	0.0050
Thrombocytopenia, % (n)	3.4 (4)	4.2 (6)	0.5031
Iron deficiency, % (n)	55.6 (80)	69.5 (82)	0.0720
Iron deficiency with anemia, % (n)	43.8 (63)	54.2 (62)	0.1495

1Results are expressed as mean ± 1 SD or as percentage (n). Abbreviations: MCV, mean corpuscular volume; RBC, red blood cells; RDW, red blood cell distribution width; SI, serum iron; TIBC, total iron-binding capacity; TS, transferrin saturation; SF, serum ferritin; CVID, common variable immunodeficiency.

2Pica items included: ice (n = 103); ice water (n = 6); salt (n = 4); sugar (n = 3); dirt, soil, or gravel (n = 3); crackers, laundry starch, pickles, or popsicles (2 each); and candy, cantaloupe, carbohydrates, carbonated beverages, chocolate-covered raisins, coffee beans, dry oatmeal, Gummi® worms, lemons, permanent markers, popcorn, raw cabbage (and broccoli and spinach), and strawberry ice cream (1 each). Some patients reported two or more pica items.

3Comparisons were made using Student's two-tailed t-test, Chi-square test, or Fisher's exact test, as appropriate.

with pagophagia than in patients with non-ice pica. Other characteristics did not differ significantly between the two patient groups (Table 2).

Univariable comparisons of subjects with and

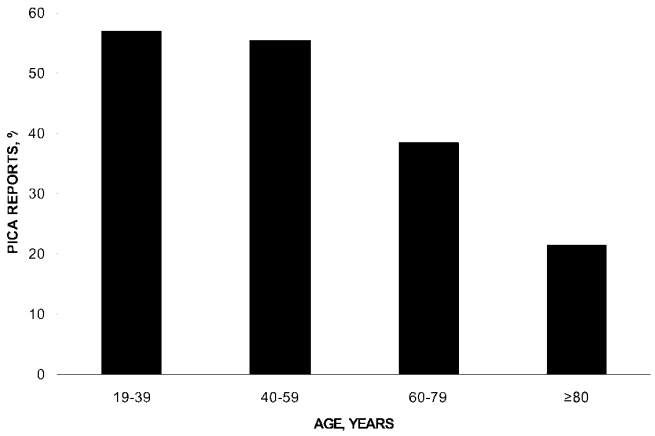

Figure 1. Frequency distribution plot of percentages of white women with pica and iron deficiency or depletion. The prevalence of pica reports was greater in women aged 19-59 years than in older women (55.9% vs. 34.8%; p = 0.0061).

without pica

Ice was the most common pica item (87.3% of patients with pica reports) (Table 3). Mean age and the prevalence of whites were lower in patients with pica than in patients without pica. The prevalence of pica reports was greater in white women aged 19-59 years than in older women (Figure 1). Cardiopulmonary symptoms and epithelial manifestations were more common in patients who reported pica than in those who did not report pica. Reproductive blood loss was more prevalent in patients with pica reports than in those without pica reports (Table 3). All patients with pica reported that their pica resolved within three weeks (or less) after administration of their first intravenous infusion of iron dextran.

Mean hemoglobin and mean MCV values were lower and mean RDW was higher in patients with reports of pica with than in patients without reports of pica (Table 3). Mean platelet counts and prevalence of thrombocytosis were higher in patients with reports of pica. Thrombocytosis occurred only in women and was more prevalent in those with pica (Table 3). Mean TIBC was higher and mean SF was lower in patients with pica reports. The prevalence of iron deficiency, with or without anemia, did not differ significantly between patients with and without pica reports. The prevalence of cancer in remission was lower in patients with pica (Table 3).

Five white women were previously diagnosed to have hemochromatosis, homozygosity for HFE C282Y, and iron overload phenotypes. They had been treated with phlebotomy to achieve iron depletion [20]. They subsequently developed iron deficiency and associated symptoms at ages 34-69 years, 2-11 years after achieving iron depletion as part of iron overload management. Their causes of iron deficiency were blood loss at total knee arthroplasty (n = 2); gastrointestinal bleeding from arteriovenous malformations (n = 1); surgery and laboratory blood loss associated with breast cancer treatment (n = 1); and chronic iron malabsorption due to gastric bypass surgery (n = 1). One of these five women reported having pica (Table 3).

Table 4. Characteristics of 14 patients with recurrent pica[1]

Characteristic	First diagnosis	Recurrence	Value of p [2]
Hemoglobin, g/dL	108 ± 16	122 ± 18	0.0500
MCV, fL	75.2 ± 9.9	81.9 ± 7.0	0.0493
RBC × 10^{12}/L	4.44 ± 0.48	4.55 ± 0.50	0.5786
RDW, %	18.7 ± 3.2	16.1 ± 2.3	0.0240
Platelets × 10^9/L	335 ± 87	311 ± 86	0.4901
Lymphocytes × 10^9/L	1.8 ± 0.7	2.0 ± 0.7	0.3808
Neutrophils × 10^9/L	4.3 ± 2.0	4.0 ± 1.7	0.6368
SI, µmol/L	7 ± 4	8 ± 4	0.8523
TIBC, µmol/L	75 ± 14	69 ± 8	0.2517
TS, %	8 ± 5	12 ± 6	0.1721
SF, pmol/L	27 ± 22	83 ± 108	0.0824

[1]Each patient had pica at first diagnosis of and at recurrence of iron deficiency or depletion. Data are presented as mean ± 1 SD. Abbreviations: MCV, mean corpuscular volume; RBC, red blood cells; RDW, red blood cell distribution width; SI, serum iron; TIBC, total iron-binding capacity; TS, transferrin saturation; SF, serum ferritin.

[2]Comparisons of mean values at first diagnosis and at recurrence of iron deficiency or depletion were made using Student's two-tailed t-test.

Recurrence of pica

Nineteen patients had recurrent iron deficiency or depletion. Fifteen had pica at first diagnosis of iron deficiency or depletion (13 white women, 1 white man, 1 black woman); 14 of the fifteen (93.3%) had pica with recurrent iron deficiency or depletion. Four other patients (all white women) did not have pica at first diagnosis; none reported pica with recurrent iron deficiency or depletion. Thus, 94.7% of these patients retained the same positive or negative pica phenotype with recurrent iron deficiency or depletion that they had at first diagnosis. The proportions of patients whose pica phenotype was the same at the initial and recurrent episodes of iron deficiency or depletion did not differ significantly (14/15 vs. 4/4, respectively; p = 0.6213, Chi-square test). At recurrence of pica, eight of fifteen subjects (53.3%) had hemoglobin and SF levels that were within the corresponding reference ranges. At recurrence of pica, mean MCV was higher and mean RDW was lower than at first diagnosis of iron deficiency or depletion; other mean CBC values and serum iron measures did not differ significantly (Table 4).

Multiple logistic regression analyses

We performed stepwise forward multiple logistic regressions using pica as the dependent variable to determine the most economical model that would include only significant explanatory independent variables. We identified four significant predictors of pica among the 31 independent variables: age and MCV (negative associations) and platelet count and RDW (positive associations) (Table 5). No other variable or combination of variables added to this four-variable model achieved statistical significance. The odds ratios and 95% confidence intervals of the four independent variables associated with reports of pica are displayed in Table 5.

Discussion

Pica was the most prevalent symptom we observed (45% of patients). In other studies of adults in the U.S., the prevalence of pica was 36-61% [8,11,13,14]. In contrast, pica was reported in only 0.6% of 353 iron-deficient subjects in Japan [15]. Ice craving (pagophagia) was reported by 87% of the present subjects who reported pica, consistent with the predominance of pagophagia among subjects with pica and iron deficiency in other reports from several countries [1,8,10,11,13,14,16,21,22].

In the present patients with pagophagia, prevalences of epithelial manifestations, chronic malabsorption, thrombocytosis, and mean MCV were lower than in patients

Table 5. Significant predictors of pica in a logistic regression model[1]

Variable	Beta coefficient	Standard error (SE)	Wald Coefficient/ SE	Probability	Odds ratio (exponential beta)	95% Confidence interval of odds ratio
age, y	-0.190	0.009	-2.242	0.025	0.981	(0.965, 0.998)
MCV, fL	-0.024	0.008	-3.119	0.002	0.977	(0.962, 0.991)
RDW, %	0.105	0.032	3.328	0.001	1.111	(1.044, 1.182)
Platelets × 10^9/L	0.002	0.001	2.288	0.022	1.002	(1.000, 1.004)

[1]These results, obtained in a forward stepwise logistic regression model, include only the significant independent predictors of pica occurrence. Abbreviations: MCV, mean corpuscular volume; RDW, red blood cell distribution width. Significance of this regression: Chi-square (4 degrees of freedom) = 30.42; probability <0.0001.

with non-ice pica. It is unknown whether differences in choices of pica items are biologically related to these manifestations. The number of patients with non-ice pica was relatively low. Further, studies involving a large number of comparisons have a high likelihood of finding statistically significant associations by chance alone (Type 1 error) [23]. Iron absorption is not significantly affected by pagophagia [24,25], and thus pagophagia is an improbable cause of iron deficiency or depletion.

The proportions of women and men who reported pica did not differ significantly. In two other studies, the prevalence of pica was significantly greater in women than men with iron deficiency [8,14]. In the present women, however, the proportion of whites with pica was significantly lower than that of blacks with pica. In a series of iron deficiency cases from South Africa, there was no significant difference in the prevalence of pica between whites and blacks [10]. We observed that the prevalence of epithelial manifestations was greater in patients with pica reports. In another study, diagnoses of fibromyalgia were significantly more prevalent in iron-deficient subjects with pica than in those without pica [26].

Pica was not significantly associated with the cause(s) of blood loss or iron deficiency or depletion in the present study. This is consistent with previous reports of pica in adults with iron deficiency due to menorrhagia or pregnancy [14]; gastrointestinal blood loss [14]; therapeutic phlebotomy for polycythemia rubra vera [27]; and malabsorption of iron due to gastric bypass [28,29]. Pica is not a predictor of the cause of gastrointestinal blood loss in persons with iron deficiency [14]. Although infection of the stomach with Helicobacter pylori was associated with autoimmune gastritis and iron deficiency in men [8,30], there was no significant association of pica with H. pylori infection in adults with iron deficiency [25].

Mean hemoglobin levels were significantly lower in the present patients with pica than in those without pica. The prevalence of anemia, iron deficiency, or iron deficiency with anemia did not differ significantly between these two groups. Patients with pica had significantly lower mean values of MCV and significantly higher mean RDW and mean platelet counts than patients without pica. Thrombocytosis was observed only in women with pica, consistent with a previous report of platelet counts in adults with iron deficiency [31,32]. In normal control subjects, mean platelet counts are also significantly higher in women than men [33]. In the present analyses, mean values of TIBC and SF were significantly lower in patients with pica than in patients without pica, but the magnitude of these respective differences was small.

Five white women in the present study were previously diagnosed to have hemochromatosis with homozygosity for HFE C282Y and were treated with phlebotomy to achieve iron depletion [20]. Later, they developed iron deficiency due to causes unrelated to therapeutic phlebotomy, like some other patients diagnosed to have HFE hemochromatosis in medical care or population screening [34-37]. The proportion of patients with reports of pica who had cancer in remission was lower than the proportion of patients without pica who had cancer in remission. In 55 unselected patients with iron-deficiency anemia due to gastrointestinal blood loss evaluated by a gastroenterology referral service at a city hospital, the proportion of patients with malignancy who had pica was significantly lower than the proportion of patients without malignancy (2/9 vs. 30/46; p = 0.0217; Fisher's exact test) [14].

Using multiple logistic regression analyses, we identified four significant predictors of pica among 31 independent variables: age and MCV (negative associations) and platelet count and RDW (positive associations). Regardless, the odds ratios associated with these variables were relatively low. Only age represents a condition that existed before the development of iron depletion or deficiency in our series of 262 non-pregnant adults. In a French study, age and sex were not significant predictors of pica in a multiple logistic regression model of observations from 79 patients with iron deficiency, although 40% of them were pregnant women [9]. The other "pre-existing" factors that were significant in our univariable comparisons (sex, race/ethnicity, cancer in remission, CVID, diabetes mellitus, and hemochromatosis) were not significant independent predictors of pica in multiple logistic regression analyses. These observations suggest that pica is triggered by factors that precede routine diagnostic indicators of iron depletion or deficiency such as abnormal CBC values or serum iron measures, or structural changes in the epithelial surfaces of the lips, oral cavity, and nasopharynx [38-42].

The present results confirm that pica develops in some adults with iron depletion or iron deficiency and not in others [8,11,13-15], although the reason(s) for this dichotomy is not reported. The concordance of recurrent pica (or absence of pica) in 19 of present patients who developed a second episode of iron deficiency or depletion was high (95%). Further, pica recurred in some of the present patients before they developed anemia or hypoferritinemia. In another study, pica was also a relatively early indicator of recurrent iron deficiency or depletion in patients who had undergone gastric bypass surgery [17]. Other investigators have reported that the occurrence of pica is not necessarily related to the severity of iron deficiency [43]. Thrombopoiesis may be stimulated by early iron depletion [44,45]. Pica in the present patients resolved rapidly after administration of intravenous iron dextran, in agreement with previous reports [4,11,12]. A genetic predisposition to develop pica in the presence of iron

deficiency or depletion could explain these observations.
Some reports including the present one suggest that certain manifestations of iron deficiency are affected by heritable traits. TMPRSS6 (OMIM *609862; chromosome 22q12-q13) encodes matripase-2 (transmembrane serine protease 6). The TMPRSS6 allele A736V (rs855791) was related to significantly lower levels of SI, TS, MCV, and hemoglobin in two genome-wide association studies of twins and general population subjects, respectively [46,47]. TMPRSS6 A736V could explain the small but significant differences we observed in mean MCV and hemoglobin levels in patients with and without pica reports, although this is unproven. RLS also occurs as an acquired manifestation of iron deficiency [19,48-50], and is cured by reconstitution of iron stores [51].
Pica ascertainment is an uncertainty in the present study. There was no ascertainment of pica based on chart review in 36.3% of the present cases; patients whose charts had no report of pica were classified as not having pica. Nonetheless, iron depletion or deficiency in all 262 patients in this study was diagnosed and managed by the same two clinicians (JCB and LFB). Accordingly, the likelihood that a distinctive symptom such as pica was not recorded in our medical records, had it occurred, is small. It was beyond the scope of the present study to attempt to contact patients without documented ascertainment of pica for further interview on this point. Uncertainties of our study also include the possibility that some patients did not report pica because they were forgetful or embarrassed [6]. Although the present patients were not treated with oral iron supplements, the proportions of present patients with pica and other manifestations of iron deficiency or depletion are similar to those in reports from North America in which oral iron supplementation was used [8,11,13,14]. Our case series included only one black man, prohibiting us from making conclusions about pica in black men. Medications such as aspirin, non-steroidal anti-inflammatory drugs, and warfarin may increase the loss of blood (and thus iron) from the gastrointestinal tract [52-57]. Other medications, including proton pump inhibitors, histamine receptor-2 antagonists, and preparations that contain calcium, may decrease iron absorption in short-term studies [58-61]. Although we did not tabulate these medications for analysis, other variables such as blood loss from different sites or chronic malabsorption were not significantly associated with increased prevalence of pica.

Conclusions

In non-pregnant adult patients with iron deficiency or depletion, lower age is a significant predictor of pica. Patients with pica have lower MCV, higher RDW, and higher platelet counts than patients without pica.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors reviewed and edited the manuscript, and all agreed with the form and content of the final manuscript. JCB (first author) designed the study, reviewed patient charts, performed statistical analyses, and drafted the manuscript. JCB (second author) reviewed patient charts, tabulated patient data, and performed statistical analyses. LFB contributed to the study design and reviewed patient charts.

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The condition of the neuromuscular system in professional lumbar sacral radiculopathy in miners

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Background.

We carried out a comprehensive analysis of all parts of afferent somatosensory systems in the presence of pain of varying severity in miners. The analysis was based on modern neurophysiological studies.

Resume. Neurophysiological changes are characterized by generalized mixed affect of the peripheral sensory nerves and 1α-afferents of H-reflex arc. The failure of systems of pain control has dominantly deafferentation character. A characteristic difference between them is also the involvement of 1β fibers (motor nerves and efferent link of the H-reflex).

Materials.

We conducted a neurological and electrophysiological examination of miners of LLP Zhezkazgan mining-metallurgical combine "Kazakhmys Corporation" and JSC "Arcelor Mittal" with the pain syndrome of vertebral pathology and lumbosacral spine who were patients in the neurological department of the clinic of the National Center of Labor Hygiene and Occupational Diseases. Control group were miners who did not have signs of pain syndrome – 28 persons. According to outpatient medical records these patients were not registered in the dispensary at the vertebral spine pathology.

All patients were divided into 3 groups on the basis of severity of a leading clinical syndrome: group 1 included 83 patients (middle age 41.8 ± 9.6 years) - not sharply expressed degree of reflex tonic pain syndrome, group 2 included 46 patients with moderate expressed degree of reflex tonic and radicular-pain syndrome (middle age 44.6 ± 11.4 years), group 3 included 19 patients (middle age 48.0 ± 10.9 years) patients with severe degree of reflex tonic.

Methods.

We conducted the symptoms complex analysis of indicators of electrophysiological studies in patients with mild to moderate degrees of pain. The control group consisted of 28 patients. To record somato-sensory evoked potentials (SSEP) we used electromyograph "Neurosoft", Russia. SSEP was recorded from the surface of the head with conventional disc electrodes with the diameter of 5 mm. When recording the potentials caused by stimulation of the right median nerve, the registration was held at Yerba (over the Brachial Plexus), C7 in the cervical (above the seventh vertebra) Fz in the frontal region, C3 and C4 (zone projection of somatosensory cortex on the left and right). The respective components were identified in trass N9 (brachial plexus response), N11-N13 (cervical segments of the spinal cord), N20-R25 (zone of the cortical projection of arm) (according to the international system of electroencephalographic leads "U-20%) when recording the potentials caused by stimulation of the left and right tibial nerve.

Statistical analysis was performed on IBM-compatible personal computer Pentium using the program Microsoft Excel and statistical analysis program AnalystSoft, StatPlus, 2007 version. A comparison between different samples of data was performed using Student's T-test for independent samples to define levels of reliability.

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Results

The problems of efficiency of prevention of pro¬fessional lumbosacral radiculopathy is the least studied in vertebro-neurology, often determined by stable high abundance and relapsing nature.

Therefore, it is necessary to assess functions of the peripheral mo¬toric systems in some professions with high risk of such disorders. For this, we studied morbidity and pathogenesis of chronic radiculopathy in Karaganda coal region on 225 patients (30-52 y.o), miners with >5 years of experience. Control group included 41 healthy non-miners (17-30 y.o). Electromyography (EMG) was conducted on 4 and 8-channel electromyo¬graphy For patients with a static-dynamic load in com¬bination to chattering, the clinic flows past rougherly, more often the pain syndrome with more expressed propulsion violations and impaired lumbosacral sys¬tem developed. For sick men with a static-dynamic load, the clinic flows past smaller percent patients with a pain syndrome is less expressed, the radicular syn¬drome flows past with a lesion in the main sensing fibres, and the lumbar part is struck. EMG biopoten¬tial amplitudes of agonists in patients with lumbosalgy of forward and back muscles were higher than in the second group. Synergists and antagonists prevail both in the forward and back groups of muscles of the lower extremities. We also showed a considerable re¬duction of miopotentials of agonist and antagonist in forward and back muscles in both groups vs. controls. Increased synergist activity was higher in the first group (vs. controls), and forward group of muscles — in the second group of patients. Thus, the considera¬ble decrease of amplitude biopotentials in agonists and antagonist forward and back muscles was accompa¬nied by increased

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amplitude of synergists, compared to the control group. Amplitudes of synergists and antagonists also prevailed for the second group, and in the back muscles of the lower extremities (except syn¬ergists of back group, which prevails for the first group). Comparing EMG data with the respective con¬trols, the considerable decrease of agonist and antago¬nist activities were seen in forward and back muscles, especially in the second group. EMG amplitude of mus¬cular biopotentials in patients with chronic radiculop¬athy with pain syndrome increased in the second group. Our study showed that the most robust differences are detected between the groups in the parameters describ¬ing excitability centers in the neuromuscular system.

In a study of indicators of SSEP it was revealed that an afferent wave of excitation, namely, pain in the ways of general sensitivity, took place in the posterior columns of the spinal cord (component N22), then through the stem sections of the brain (component N30) and later in cortex (a component of P38, P46). These curves reflect the passage of the nerve impulse to the relevant structures and can detect subclinical slowing of the pulse indicating the failure of the conduction system.

We revealed the increase of amplitude of characteristics depending on the pain, but it is more expressed in mild to moderate degrees of pain. The amplitude of the component N30 representing the activation of the posterior columns of the spinal cord at the border of the cervical spine and medulla oblongata with mild to moderate degree increased.

Indicators of the amplitude component P38 and 46 reflecting the activation of the somatosensory cortex had tendency to increase at a moderate and significant degree of pain.

Thus, increasing the components of SSEP amplitude, interval, latency in patients with apparent pain syndrome, depression and anxiety may indicate the development of central sensitization of the conduction system (N30, P38, P46), realized in nonspecific mediobasal limbic structures of the brain [2, 7, 8].

N10-N20 intervals characterize the conduction on the ascending pathways of the spinal cord, the interval N20-P30 is similar to the central conduction time (CCP).

In patients with the moderate degree of pain there was a significant lengthening of the intervals: N13; N13 – N20; N20 – N30. These indicators have most significantly increased in the apparent degree of pain. The increase of the interval N22-P38 with the preservation of CCP indicating a violation of the ascending pathways of the spinal cord, depending on the severity of pain in patients with vertebral lumbar pathology was marked.

In patients with vertebral pathology with mild pain syndrome there was a significant increase in latency of N30 with a tendency to increase the component P38, P 46, and in patients with mild to moderate degree of pain there was a significant lengthening of the latency of components N22, N30, P38, P 46.

In patients with vertebral pathology with moderate and severe pain syndrome there was a significant increase in latency of components N22, N30, P38, P46, respectively, characterizing the intensification of the processes of inhibition of neural structures of the spinal cord.

Also, in patients with apparent pain syndrome there was a significant increase in the duration of intervals of absolutely all the components, indicating exhaustion and desynchronization of the higher antinociceptive centers.

In patients with mild to apparent degree of pain we revealed a significant lengthening of N22 latency respectively, that is characterizing the affect of fibers of peripheral sensory fibers (decrease in SSEP) of 1a-afferents of the H-reflex arc and L3-L4 afferents demyelination on a spinal level (data of SSEP study with stimulation of n. tibialis).

Thus, the idea of understanding the mechanisms of the production factors influence on the severity of clinical manifestations with pain syndrome in vertebral pathology in miners at the level of the afferent somatosensory system was enhanced in the scientific work.

Conclusions.

1. Revealing of change of indicators SSEP at vertebral pathologies and lumbosacral spine level at miners, are criterion of diagnostics character degree of expressiveness painful syndrome.

2. The developed criteria diagnostics of infringements painful sensitivity do possibility to spend the differential diagnosis of frustration in clinically not clear cases.

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Phenylcarboxylic acids as potential markers for diagnosis of sepsis in cardiac surgery patients

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Abstract

Objectives. Complex pathophysiological mechanisms of severe sepsis still remain unclear despite current intensive research and success achieved in its treatment and diagnostics. Our previous screening of microbial aromatic compounds showed increased level of several phenylcarboxylic acids (PCAs) in blood of septic patients, namely: p-hydroxyphenyllactic acid (HPLA), phenyllactic acid (PLA) and p-hydroxyphenylacetic acid (HPAA). The objective of the present study is to identify the threshold values of PLA, HPLA and HPAA for sepsis diagnostics and to evaluate the sensitivity and specificity of these markers.

Design and methods. Total 264 blood samples from 25 healthy volunteers and 175 adult patients of cardiovascular surgery clinic were evaluated. Blood concentrations of PCAs were determined by gas chromatography-mass spectrometry.

Results. Increased levels of HPAA, HPLA and PLA were observed in the group of patients with severe sepsis. Moreover, significantly higher levels of PLA, HPLA were found in non-survivor patients with sepsis. The threshold blood concentrations of HPAA, HPLA and PLA for sepsis diagnostics were estimated as 8 μM, 3 μM and 1 μM respectively.

Conclusions. Detection of PLA, HPLA and HPAA in blood in concentrations higher than the determined threshold levels may suggest presence of sepsis. Therefore, these compounds could be proposed as sepsis markers for use in clinical practice.

Keywords:

Phenylcarboxylic acids, Phenyllactic acid, p-hydroxyphenyllactic acid, p-hydroxyphenylacetic acid, Sepsis diagnostics, Microbial biomarkers

Introduction

Early diagnosis of sepsis is crucial for adequate management of critically ill patients. Severe bacterial infections and sepsis with multiple organ failure (MOF) are major causes of morbidity and mortality in ICU [1-3]. The relevance of clinical and laboratory signs, such as body temperature, tachycardia, respiratory rate and leukocytes count, is low because of their poor specificity for the sepsis diagnostics especially in critically ill patients who often have SIRS without infection. It is often difficult to diagnose sepsis accurately in ICU patients with major trauma, massive tissue injury in abdominal and cardiothoracic surgery, ischemic injury, in critically ill patients with MOF, as clinical and laboratory symptoms in such patients with severe impairments and lesions can overlap with signs of SIRS, i.e. increased levels of biomarkers can be associated either with sepsis or concurrent diseases and conditions. Therefore, laboratory diagnostics of sepsis needs to be improved [4, 5].

When bloodstream specific microbial components are recognized by immune system the latter responds with exaggerated production of mediators and cytokines, ultimately resulting in severe sepsis and septic shock. Thereby microbial components and cytokines can be used as markers (biomarkers) for diagnosis of sepsis [6].

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Blood culture is still widely used in microbiological laboratories for diagnosis of bloodstream infections and sepsis in all suspected cases despite the fact that this method often yields false-negative results. Novel molecular diagnostic technique that has emerged quite recently in clinical practice is nucleic acids testing (NAT-methods) for pathogen detection in sepsis [7]. Detection of microbial DNA in blood specimens seems to be more sensitive and specific than performance of routine blood cultures. However, NAT allows to determine the etiology of bacteremia, but doesn't answer the question whether sepsis is present or not.

Clinical relevance of numerous "indirect" biomarkers for sepsis such as C-reactive protein (CRP), procalcitonin (PCT), interleukins (IL-6, IL-8), LPS-binding protein, neopterin, macrophage migration inhibitory factor (MIF), soluble urokinase-type plasminogen activator receptor (su-PAR), soluble triggering receptor expressed on myeloid cell-1 receptors (s-TREM) and other molecules of immune response has being evaluated for diagnosis of sepsis. Each of them has certain advantages and limitations. The most important question to be answered is whether these markers have a potential to clearly differentiate patients with SIRS from patients with bacterial sepsis [8].

Some authors propose to use combinations of biomarkers to improve diagnosis accuracy, as well as prognosis, treatment efficacy and thereby clinical outcomes and survival rates [9, 10].

It has been shown earlier that metabolites of live microorganisms could be used as potential biomarkers ('direct' markers) of bacterial infection [11]. For example, volatile fatty acids (VFA) are specific metabolites of some anaerobic bacteria. Determination of VFA (acetic, butyric, propionic acid and others) in blood and other clinical specimens is routinely used for diagnosis of anaerobic infection [12]. Detection of long-chain fatty acids (10Me18) is used to identify mycobacteria in culture isolates and clinical specimens [13, 14].

We suggested that clinically relevant molecules for diagnosis of bacterial infection can be found among phenylcarboxylic acids. It is well established that phenylcarboxylic acids are formed during degradation of aromatic amino acids by human gut microflora [15]. Our screening of microbial compounds

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has demonstrated that levels of p-hydroxyphenyllactic acid (HPLA), phenyllactic acid (PLA) and p-hydroxyphenylacetic acid (HPAA) were increased in blood of patients with severe sepsis [16, 17]. Our in-vitro studies showed that sepsis-related bacteria, such as Klebsiella pneumonia, Escherichia coli, Staphylococcus aureus, also produce PCAs [18].

The objective of the present study is to estimate threshold blood levels of PLA, HPLA and HPAA for sepsis diagnostics in post-surgery ICU patients, and to determine sensitivity and specificity of these markers.

Materials and methods

Patients

Adult patients underwent cardiac surgery between 2005 and 2007 at the Bakoulev Scientific Center for Cardiovascular Surgery, Russia, were enrolled in the study. The main inclusion criteria were clinically suspected or documented infection and/or sepsis in ICU patients diagnosed by attending doctor. Patients were included into the study at the moment of blood collection for PCT and blood-culture analyses. Some portion of blood were stored for further (retrospective) PCAs analysis. Patients were divided into groups after retrospective analysis of patients' medical records and estimation of clinical and laboratory signs of infection and/or sepsis at the moment of blood collection. The analysis of all patient's records included following documented clinical parameters: age, gender, vital signs, clinical status, severity of patients' condition and routine laboratory parameters. PCT-tests were repeated in cause of SIRS recurrence in patients.

Groups

Group (No. 1) – patients with severe sepsis (n=35). Patients of ICU on artificial lung ventilation (ALV), with documented source of infection, SIRS, MOF and clinical diagnosis of sepsis made by attending doctor. The following criteria were used for the definition of sepsis: clinical signs of SIRS (two out of the four following parameters: white cell count above 12 x 10^9/L or below 3 x 10^9/L or the presence of > 10% band forms, temperature above 38°C or below 36°C, tachycardia (>90 beats/minute) or tachypnoea (>20 breaths/minute)) with documented source of infection (pneumonia, wound fever, bacteremia). Severe sepsis was defined as sepsis with clinical manifestations of multiple organ failure, according to consensus criteria ACCP/SCCM [19].

Comparison Group (No. 2) – patients with local infection (n=35). Patients with documented source of infection (pneumonia, wound fever, bacteremia), without clinically established and recorded SIRS and sepsis diagnoses.

Comparison Group (No. 3) – patients with non-infectious complication (n=33). Patients with prolonged ICU stay on ALV, with some signs of SIRS and/or clinically suspected infection at the moment of taking blood sample, confirmed in the further monitoring as a cases of cardiopulmonary decompensation, encephalopathy or renal/hepatic failure without any infectious component.

Comparison Group (No. 4) – patients with smooth recovery (n=30). Patients with ICU stay < 24 hours and discharge from the hospital after surgery without any complications. Blood samples from these patients were collected twice on Day 3 and Day 6 after operation.

Control Group (No. 5) – patients before surgery (n=42). Patients with valvular or coronary heart diseases without clinical or laboratory signs of infection, whose blood samples were collected at the moment of admission to the hospital (i.e., before surgery).

Control Group (No. 6) – healthy volunteers (n=25). Healthy and able to work individuals without any signs of infection or any other disease at the moment of collecting blood specimen and during first 7 days afterwards.

Blood samples

Blood specimens of patients with confirmed or suspected bacterial infections were evaluated for blood culture (BacTAlert, BioMérieux, France) and for procalcitonin level (BRAHMS PCT LIA, BRAHMS Aktiengesellshaft GmbH Germany).

Blood samples for PCA analyses were collected into sterile tubes without anticoagulant and centrifuged at 800g for 15 min. Obtained serum supernatants were stored at -70 °C until analysis.

GC-MS analysis

The mixture of 0.2 ml of serum and 0.8 ml of water was adjusted to pH 2 with sulfuric acid. Solution of D5-benzoic acid in ethanol (400 ng in 10 ml) was added as internal standard. Obtained mixture was extracted with diethyl ether (2 x 1 ml). Ether extract was evaporated until dry at 40°C and treated by 20 µl of N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) at 80°C during 15 min. to produce trimethylsilyl-derivatives (TMS-derivative) of PCAs. The resulting specimens of silylated phenylcarboxylic acids were dissolved in 80 µl of hexane and analyzed by the GC-MS method.

Samples were analyzed for PCA content using Agilent 6890/5973 gas chromato-mass spectrometer (Agilent Technologies, USA) in the full scan mode. The components were chromatographically separated in a HP5MS quartz capillary column, 0.2 mm inner diameter, 25 m in length, with film thickness of 0.33 µm. The carrier gas was helium with a flow rate of 1.2 ml/min. The temperature parameters during analysis were as follows: evaporator temperature – 280°C; initial temperature of column thermostat 80°C was held for 4 min; then temperature was increased to 240°C with rate 7°C/min and then to 320°C with rate 15°C/min, and was held until the end of the analysis. Injected sample volume was 2 µl and total time of analysis – 35 min; detector operation delay time – 4 min. Quantity of detected compound was estimated by comparing its peak area with that of a standard, i.e. TMS-derivative of D5-benzoic acid (retention time 10.45 min), with known concentration (400 ng in 10 ⊠l). Phenylcarboxylic acids were identified based on the retention time (RT) for both basic and additional ions (m/z), as shown in Table 1.

Table 1. Retention time, intensity of basic and additional ions (m/z) for TMS-derivatives of phenylcarboxylic acids (PCAs).

Compound	Retention time of TMS-derivative, min.	Basic ion (m/z), a.u.	Additional ion (m/z), a.u.
D5-benzoic acid (standard)	10.45	184	110
p-hydroxyphenyllactic acid (HPLA)	22.02	179	147
phenyllactic acid (PLA)	17.12	193	147
p-hydroxyphenylacetic acid (HPAA)	18.04	179	296

Chemicals

p-Hydroxyphenylacetic acid, p-hydroxyphenyllactic acid, phenyllactic acid (Fluka). N,O-Bis(trimethylsilyl)

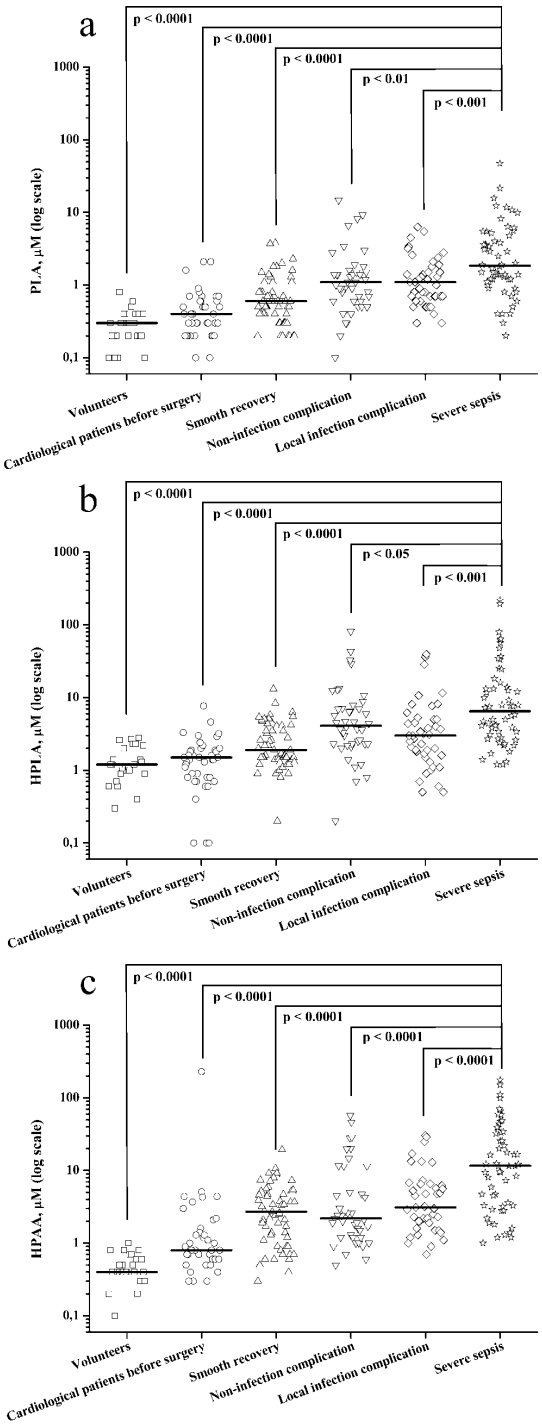

Fig 1. Serum concentration of phenylcarboxylic acids. a - phenyllactic acid (PLA), b - p-hydroxyphenyllactic acid (HPLA), c - p-hydroxyphenylacetic acid (HPAA). The horizontal bars represent the mean level for each group.

trifluoroacetamide (for GC, Fluka), diethyl ether (Acros Organics), D5-benzoic acid (Acros Organics) , Ethanol (Sigma-Aldrich).

Statistical analysis

Data are expressed as a median (IQR-interquartile range). Nonparametric Mann-Whitney U test was used for comparison of study and control groups ($p < 0.05$ was considered as statistically significant). Receiver operating characteristic (ROC) curves were constructed using MedCalc for Windows (version 10.2.0.0). ROC curve analysis was used to estimate an optimal cut-off value for the serum PCAs concentrations for diagnosis of sepsis as well as for determining the sensitivity and specificity of the test.

Results

Totally 25 healthy individuals and 175 patients with heart diseases, including 42 patients before surgery, 30 patients with smooth recovery without complications and 103 patients with different complications after cardiac surgery were enrolled into the study.

Main baseline characteristics of the patients are presented in Table 2. All groups were comparable regarding age and gender, with the exception of a group of healthy volunteers, who were significantly younger. Groups were also comparable by types of surgery performed. Mortality rate was 27 % (47/175). Mortality in the group of severe sepsis (including septic shock) reached 57 % (20 out of 35).

Totally 197 blood samples were obtained from 103 patients who underwent surgery. The following signs of SIRS after surgery at the moment of blood collection were observed: fever > 38°C – in 61 (31%), hypothermia < 36°C – in 5 (3%), leukocytosis > 12 x 10^9/L – in 92 (47%), leucopenia < 4 x 10^9/L – in 11 (6%), band form > 10 % – in 29 (15%). Symptoms of organ failure were presented in the majority of patients, including cardiovascular – 102 (52%), respiratory – 110 (56%), renal – 56 (28%), hepatic – 26 (13%), and cerebral – 61 (31%).

Bacteremia was documented in 19 (10%) cases. The most frequently detected pathogens isolated from blood cultures were Klebsiella pneumonia and Staphylococcus sp. (11 and 7 cases, respectively).

Local source of infection was documented in 88 cases, in most cases it was ventilator associated pneumonia (VAP) (83 patients).

Positive cultures were observed in 58 cases (19 bacterial cultures from blood specimens and 39 bacterial cultures from other clinical specimens, i.e. bronchoalveolar lavage, wound pus). Gram-negative bacteria were identified in 41 cases, and gram-positive bacteria – 17 cases.

In the group No1 (severe sepsis) levels of PCT were > 2 ng/ml, PCT levels reached > 10 ng/ml in > 50 % of all patients. Although increased PCT levels were also observed in patients from other groups, namely: PCT > 2 ng/ml was observed in 54.8 % (46/84) patients with post-surgery complications without sepsis (groups No2 + No3). In group No4 (smooth recovery) only 10 % (3/30) of patients had PCT levels > 2 ng/ml. (see Table 2).

The measured levels of phenylcarboxylic acids (PCAs) in two control groups (No5 – before surgery and No6 – healthy) were as follows: HPAA – 0.8 (0.5-1.4) and 0.4 (0.4-0.6) µM, respectively; HPLA – 1.5 (0.8-2.0) and 1.2 (0.9-2.0) µM, respectively; PLA – 0.4 (0.2-0.6) and 0.3 (0.2-0.4) µM, respectively. The levels of PCAs in these groups had no statistically significant difference. Levels of PLA, HPLA and HPAA in the severe sepsis group were obviously higher then in all other groups, i.e. 1.8 (1.1-4.9), 7.5 (3.0-14.4) and 11.6 (3.3 -33.6) µM, respectively, with confirmed statistical significance $p<0.0001$ (see Figures 1a, 1b and 1c, correspondingly). Comparison of survivors and non-survivors in the severe sepsis group yielded significant difference for PLA (1.2 (0.8-1.6) vs. 3.6 (1.5-6.4) µM, respectively) and HPLA (2.8 (2.2-5.0) vs. 12.5 (5.6-34.7) µM, respectively), but not for HPAA (see Figures 2a, 2b and 2c, correspondingly).

Receiver operating characteristic (ROC) plot analysis (see Figure 3) was performed to define an optimal diagnostic threshold for HPAA, HPLA and PLA values in septic patients. Performance of serum levels HPAA, HPLA and PLA for the

Table 2. Clinical characteristics of patients' population and serum samples.

*Groups' names: 1 – volunteers, 2 – cardiological patients before surgery, 3 – smooth recovery, 4 – non-inflectional complications, 5 – local infection complication, 6 – severe sepsis. * - Rates of positive blood cultures. ** - Rates of positive cultures, samples include sputum, urine and other tissues.*

Group Number		1	2	3	4	5	6
Number of patients (N)		35	35	33	30	42	25
Patients background							
Mean age (years±SD)		54±8	53±8	53±12	50±11	49±11	37±12
Gender	Male	25 (71%)	22 (63%)	19 (59%)	21 (70%)	26 (62%)	9 (36%)
	Female	10 (29%)	13 (37%)	13 (41%)	9 (30%)	16 (38%)	16 (64%)
Type of surgery	Valve replacement	16 (46%)	23 (66%)	23 (70%)	20 (67%)	30 (71%)	-
	Bypass	11 (31%)	6 (17%)	4 (12%)	1 (3%)	0	-
	Valve+Bypass	8 (23%)	6 (17%)	6 (18%)	9 (30%)	12 (29%)	-
Outcome	Survive	15 (43%)	22 (63%)	19 (58%)	30 (100%)	-	-
	Non-survive	20 (57%)	13 (37%)	14 (42%)	0	-	-
Serum samples (n)		56	42	42	57	42	25
PCT, ng/ml	<0.5	0	5 (12%)	4 (10%)	41 (72%)	39 (93%)	-
	0.5-2	0	18 (43%)	11 (26%)	13 (23%)	3 (7%)	-
	2-10	18 (32%)	12 (29%)	16 (38%)	2 (4%)	0	-
	>10	38 (68%)	7 (17%)	11 (26%)	1 (2)	0	-
Clinical characteristics of patients at the time blood collections							
T, °C	>38	28 (50%)	17 (40%)	16 (38%)	0	0	-
	<36	3 (5%)	0	2 (5%)	0	0	-
Le, x109 /L	>12	34 (61%)	34 (81%)	24 (57%)	0	0	-
	<4	9 (16%)	0	2 (5%)	0	0	-
Band forms	>10%	17 (30%)	5 (12%)	7 (17%)	0	0	-
MOF	Cardiac	41 (73%)	30 (71%)	31 (74%)	0	0	-
	Respiratory	52 (93%)	40 (95%)	18 (43%)	0	0	-
	Renal	32 (57%)	12 (29%)	12 (29%)	0	0	-
	Hepatic	14 (25%)	4 (10%)	8 (19%)	0	0	-
	Cerebral	27 (48%)	14 (33%)	20 (48%)	0	0	-
Positive bacteriemia*	Gram positive	5 (9%)	3 (7%)	-	-	-	-
	Gram negative	10 (18%)	1 (2%)	-	-	-	-
Positive culture**	Gram positive	2 (4%)	6 (14%)	1 (2%)	-	-	-
	Gram negative	13 (23%)	14 (33%)	3 (7%)	-	-	-
Documented source of infection		46 (82%)	42 (100%)	0	0	0	-

diagnosis of sepsis are shown in Table 3.

The optimal threshold for HPAA was found to be as high as 8 μM (with sensitivity of 64.3 %, and specificity of 88.9 %), for HPLA – 3 μM (sensitivity 75.0 % , specificity 66.4 %), for PLA – 1 μM (sensitivity 75.0 %, specificity 71.6 %).

Discussion.

Our data demonstrate that the levels of mentioned above PCAs strongly correlate with presence and the severity of sepsis. Two important findings should be mentioned:

1. Levels of PLA, HPLA and HPAA are significantly higher in septic patients compared to patients in all control groups (healthy volunteers and patients before surgery) and all comparison groups (patients after cardiac surgery without complications, with local infection and with non-infection complications).
2. Levels of PCAs in severe sepsis group were substantially higher in non-survivor compared to survivor patients.

These findings support our suggestion to consider PLA, HPLA and HPAA as diagnostic markers of sepsis.

Our study deals with evaluating PLA, HPLA and HPAA levels in blood of septic patients. Subject of inquiry were cardiovascular patients undergoing cardiopulmonary bypass surgery. Cardiac surgery using cardiopulmonary bypass induces a non-specific acute inflammatory response. PCT-test is low-specific for diagnostics of sepsis and non-septic SIRS in this cohort since these patients are undergone surgical trauma, massive transfusion, blood loss, hypothermia during operation [20]. So, sepsis diagnostics in this particular cohort of patients is the most challenging and vitally important task.

Sensitivity and specificity of proposed method are significant for the compounds to be used as biomarkers (sensitivity and specificity for PLA threshold concentration 1 μM are 75.0 % and 71.6 %; for HPLA 3 μM – 75.0 % and 66.4 %; and for HPAA 8 μM – 64.3 % and 88.9 %, respectively). When recruiting patients into the group of severe sepsis we used documented diagnosis of sepsis made by attending doctor according to habitual routine criteria (local source of infection or positive blood-culture plus more then two symptoms of

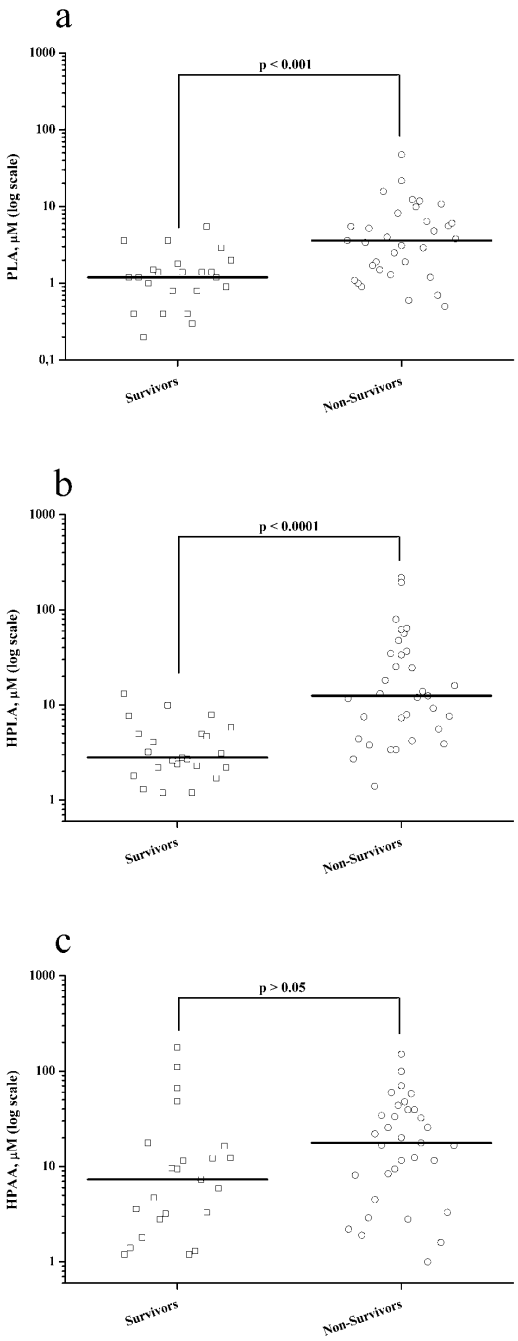

Fig 2. Serum concentration of phenylcarboxylic acids. a - phenyllactic acid (PLA), b - p-hydroxyphenyllactic acid (HPLA), c - p-hydroxyphenylacetic acid (HPAA) in surviving versus nonsurviving patients with severe sepsis. The horizontal bars represent the mean level for each group.

SIRS). However, data from Table 2 indicate that some of the patients from group No2 (local infection) and group No3 (non-infectious complications) probably also had sepsis. These patients were not included initially into severe sepsis group because they failed to fit the relevant criteria at the time of enrollment, i.e. moment of taking first blood sample according to the study protocol. Thus, our study protocol could be excessively tough.

Sensitivity, specificity and ROC values for each of investigated PCAs were similar. There is a direct correlation among HPAA PLA (Spearman R = 0.71, $p < 0.05$); PLA – HPLA (R = 0.84, $p < 0.05$); HPAA – HPLA (R = 0.70, $p < 0.05$). In theory, any of the PCAs can be used alone as a marker of sepsis, although additional clinical studies are required to define the best one.

Our study has some limitations. We suppose that it is possible to increase the sensitivity and specificity of markers using common recruiting criteria to include patients with sepsis of another genesis. Since our clinical non-randomized study was held in just one cardiovascular surgery hospital, it is still unclear whether these data could be valuable in ICU of different profiles and in other heterogeneous groups of patients with severe sepsis. Moreover, in our study levels of PCAs were measured retrospectively, thus it remains unclear whether obtained results could influence the clinical decisions in questionable cases.

PCAs can be named as «direct» markers of sepsis because of their microbial origin. All detectable blood PCAs are associated exclusively with metabolites of living bacteria. It has been demonstrated earlier that PLA and HPLA are produced in vitro via degradation of phenylalanine and tyrosine by enterobacteria (for example, Klebsiella pneumonia, Escherichia coli), Staphylococcus aureus and some other bacterial species [18].

It is important that increased levels of PLA, HPLA and HPAA were observed in all septic patients without exception. PCAs involvement in pathogenesis of sepsis seems to be very plausible. Preliminary experimental data demonstrated that some PCAs, including PLA, HPLA and HPAA, have toxic effects on mitochondria: at concentrations of 0.01 – 0.1 mM. PCAs caused the decrease in rate of oxidation of NAD-dependent substrates, activation of Ca^{2+} menadione-induced opening of the cyclosporin A-sensitive pore and the production of reactive oxygen species (ROS). Progression to mitochondrial failure caused by toxic effects of PCAs could possibly explain the phenomenon of mitochondrial dysfunctions in sepsis [21].

Therefore, based on all mentioned data we hypothesize the important role of PCAs in sepsis.

Conclusion

Severe sepsis is the most common cause of mortality in critically ill patients. Most of patients usually have increased levels of practically whole spectrum of «indirect» biomarkers even in the absence of infection. Under these circumstances new more reliable and relevant "direct" markers are required for improvement of sepsis diagnostics. Several microbial metabolites seem to be very promising for this purpose. Particularly, PCAs attracted our attention because numerous sepsis-related bacteria appeared to produce these metabolites via degradation of aromatic amino acids (phenylalanine and tyrosine).

We detected significantly increased levels of HPAA, HPLA, PLA in all septic patients versus healthy individuals or non-septic patients. Levels of PCAs reflected the severity of sepsis and were significantly higher in non-survivor versus survivor patients with sepsis.

We suppose that each of studied PCAs (HPAA, HPLA or PLA) can be used as a direct marker of sepsis in patients after cardiovascular surgery. Future clinical studies are required for validation of these PCAs as new markers of sepsis in different categories of patients (for example, patients after severe trauma and burn injuries, with hematological malignancies, skin/soft tissue infections, after abdominal surgery, etc).

Acknowledgments.

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Table 3. Performance of serum HPAA, HPLA and PLA for the diagnosis of sepsis.

Phenylcarboxylic acid	Criterium values, μM	sensitivity, %	95% confidence interval	specificity, %	95% confidence interval
HPAA	> 1	98.2	90.4 – 99.7	37.5	30.9 – 44.5
	> 3.1	78.5	65.6 – 88.4	67.8	61.0 – 74.1
	> 8	64.3	50.4 – 76.6	89.0	83.9 – 92.9
HPLA	> 1.1	100.0	93.6 – 100.0	22.1	16.7 – 28.4
	> 3	75.0	61.6 – 85.6	66.4	59.5 – 72.7
	> 7.9	39.3	26.5 – 53.2	91.4	86.7 – 94.8
PLA	> 1	75.0	61.6 – 85.6	71.6	65.0 – 77.7
	> 3	39.3	26.5 – 53.2	94.2	90.1 – 97.0
	> 8.2	12.5	5.2 – 24.1	99.0	96.9 – 99.9

their participation in the study, Katherina Chernevskaia for performing PCT measurements, Tatiana Vostrikova for microbiological monitoring and Dmitry Popov for helping with patients recruitments.
Conflict of interest: No conflict of interest to declare.

List of abbreviations.

ALV – artificial lung ventilation
BSTFA – N,O-bis(trimethylsilyl)trifluoroacetamide
DNA – deoxyribonucleic acid
GC-MS – gas chromatography mass-spectrometry
HPAA – p-hydroxyphenylacetic acid
HPLA – p-hydroxyphenyllactic acid
ICU – intensive care unit
IQR – interquartile range
LPS – lipopolisaccharide
MOF – multiple organ failure
NAT – nucleic acids testing
PCA – phenylcarboxylic acids
PCT – procalcitonin
PLA – phenyllactic acid
ROC – receiver operating characteristic
RT – retention time
SIRS – systemic inflammatory response syndrome
su-PAR – soluble urokinase-type plasminogen activator receptor
TMS – trimethylsilyl
VAP – ventilator associated pneumonia
VFA – volatile fatty acids

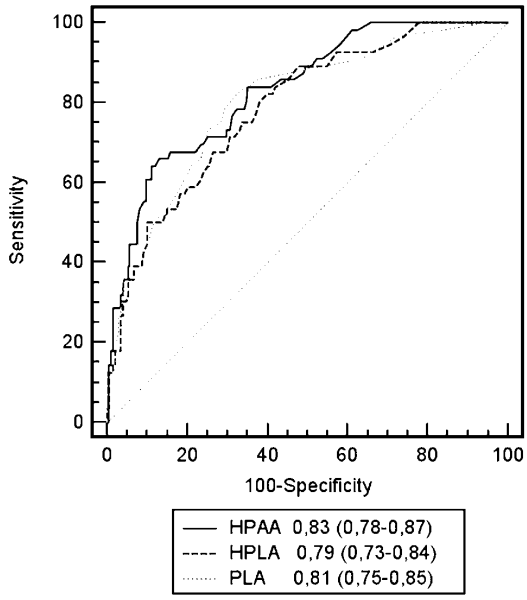

Fig 3. Sensitivity and specificity of phenyllactic acid (PLA), p-hydroxyphenyllactic acid (HPLA), p-hydroxyphenylacetic acid (HPAA) as biomarkers for sepsis diagnostics. The areas under receiver operating characteristic curve are given with 95% confidence intervals.

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Audio-visual technologies in medical rehabilitation of chronic stressful conditions and psychosomatic diseases

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Nowadays people develop lingering stress-reactions against the background of significant informational and social overstrain. It causes a considerable decrease in working capacity and quality of life, causes conditions for rapid development of chronic somatic illnesses with severe impairment of the cardio-vascular, immune, endocrine, central and vegetative nervous systems. Rehabilitation of patients after distress is very complicated. Among up-to-date non-medicamental technologies allowing to arrest effectively stress-reactions and distress and their consequences, a group of audio-visual technologies comes to the front. In particular, we developed a methodology of polysensor relaxation and put it in practice with the help of the apparatus called "RHYTHM-POLYOT". The methodology of polysensor relaxation is based on concurrent rhythmic light and sound influence on patients' visual and auditory analyzers. The copyrighted programme is aimed at correcting their psycho-emotional condition and increasing their working capacity (Patents RU 2103038 C1.27.01.1998; RU 174 25 U 1. 10.04.2001).

The following principles underlie the methodology: bioresonance, fiziogichnost, and individualization of influence achieved by a change in the frequency and rhythm of sound and light signals subject to the initial condition of the patient with the help of feedback. The technology has been certified and recommended to implementation by the Ministry of Public Healthcare and Social Development of the Russian Federation. The "Rhythm-Polyot " apparatus in which the technology of polysensor relaxation is put in practice was awarded gold medals and diplomas at the SALON MONDIAL DE L'INVENTION,DE LA RECHERCHE ET DE L'IN NOVATION INDUSTRIELLE, an international exhibition-saloon (Brussels,1995, 2004), at the 3d International Saloon of Innovations and Investments (Moscow, 2003), at the Lepin's Exhibition of French Inventors and Manufacturers(Charlerou, 2004).

The present study is aimed at the assessment of clinical efficiency of polysensor relaxation on medical rehabilitation of patients with psychosomatic illnesses (essential hypertension, initial forms of brain blood supply deficiency (IFBBSD), discirculatory encephalopathy in the second stage in working people).

Methods: clinical, clinical neurological, biochemical, ECG, REG, EEG, WAM (wellbeing, activity, mood) and life quality scores, questionnaires for the assessment of the vegetative status, R. Foll's electropunctural diagnostics.

Results: We evaluated the effectiveness of a course treatment by polysensor relaxation in 3 main groups and the condition of the patients in the corresponding control groups (without biorhythmic stimulation). Group 1 included patients with essential hypertension in I and II stage (45 subjects). Group 2 included patients with initial forms of brain blood supply deficiency (IFBBSD) (47 subjects). Group 3 included patients with discirculatory encephalopathy in the second stage (52 subjects).

Background medicamental therapy was standard in all the groups.

On completion of the course of polysensor relaxation we registered reliable normalization of heart rate, respiration rate, arterial blood pressure (systolic pressure decreased by 7-12 mm Hg, diastolic pressure decreased by 5-7 mm Hg), a decrease in the intensity of headaches by 30% in comparison with control patients, a decrease in the intensity of dizziness and ear noise and tinnitus cerebri, normalization of memory and attention (Table 1), readings on the rating scale of wellbeing, activity, mood (WAM), considerable improvement of the sleep, less marked pain in the cervical and thoracic spine. We also registered an increase in critical frequency of flicker fusion (CFFF) by 5-12% in comparison with control patients, normalization of biophysical readings in acupunctural points (in projection points of the nervous and endocrine systems and points of the connective tissue in 68.5% patients in Group 1, 72.9% patients in Group 2 and 70.5% patients in Group 3). In the control groups these readings were 39.35%, 27.6% and 33, 4% respectively

Table 1. Study of the function of attention according to the results of Schulte test in patients with IFBBSD before and after

treatment by the method of polysensor relaxation (M+m)

Readings (sec)	Main group		Comparative group	
	Before treatment	After treatment	Before treatment	After treatment
Average time	58,7±3,9	41,6±2,1*	59,1±4,1	53,1±3,2
Total time	278,9±6,8	218,7±4,1*	299,8±6,9	247,3±2,1

*Note: * - significant difference before and after treatment p<0.05*

Table 2 Dynamics of the readings of lipid exchange in patients with IFBBSD in the main group before and after treatment by the method of polysensor relaxation (M+m)

Readings	Before treatment	After treatment
Cholesterol mole/l	5,31±0,27	4,37±0,17
Alpha-LP mole/l	1,01±0,05	0,09±0,02
Beta-LP g/l	4,88±0,39	4,44±0,22
Triglycerides mole/l	1,72±0,20	1,57±0,16

*Note * -significant difference before and after treatment p<0.05*

According to the rheoencephalography (R.E.G), evidence of signs of dystonia by hypertonic type and asymmetry of the blood flow in patients of main Groups 1, 2 and 3 reliably decreased, normalization of the venous outflow and a decrease in the degree of asymmetry of the blood flow were noticed, improvement of elasticotonic properties of the vascular wall was registered

The readings of electroencephalography (EEG) in the main groups were evidence to the regulating influence on the whole frequency spectrum in the frontal leads (theta-, alpha- and beta-rhythms), i.e. EEG-criteria suggest optimization of wakeful state and activity (alpha-rhythm), mental activity (theta- and beta-rhythms) in 68.3% patients on average. In comparison groups reliable distinction from the initially registered data was not revealed.

Thus, the audio-visual technology, implemented through the "RHYTHM-POLYOT" apparatus can be used with the aim of health improvement of the able-bodied population who need rapid recovery of their emotional, mental and physical condition as well as treatment and medical rehabilitation of patients with psychosomatic diseases. The therapeutic efficacy of the method is confirmed by the proved clinical efficiency of the technology and reliable and lasting effect of the therapeutic afteraction, that is normalization of the parameters of biochemical and biophysical homeostasis within 4 – 6 months after a course of treatment.

The obtained results are evidence of high efficiency of this method in medical rehabilitation of patients with psychosomatic diseases and illnesses of aging aimed at the improvement of life quality and recovery of working capacity in terms of normalization of psycho-emotional condition, vascular tone of the brain, the condition of the vegetative nervous system, electric activity of the cerebral cortex, the levels of arterial pressure.

Medical rehabilitation of cervical vertebral syndromes in females using low-frequency magneto-light therapy combined with acupuncture

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Currently it is relevant research of new techniques of medical rehabilitation of cervical vertebral syndromes (CVS) in females taking into account individual characteristics of pathology development.

Goal: estimate clinical efficacy of method combining low frequency magneto-light therapy and homeopathic preparations "Traumeel S", "Zeel T", "Discus compositum" in medical rehabilitation of female patients with cervical vertebral syndromes.

Research method: Our study included 80 female with vertebral syndromes of neck (G54, G55, M42, M43 by ICD 10). In 100% cases patients were in the subside phase of the disease. Average age of patients was 51.7 ± 1.6 years, average history of illness 12.5 ±1.6 years. Time period from the moment of desease development to start of medical rehabilitation was 2-3 weeks. Patients were split into two groups, comparable by age and clinical picture. First group formed 40 females with related diseases and intolerance to standard drug and physical electro-therapy. First group received low-frequency magneto-light therapy with "Master – MST – 01" apparatus into neck zone plus paravertebral (C2-C6) in combination with pharmacological acupuncture together with homeopathic preparations "Traumeel S", "Zeel T", "Discus compositum" and classic methods acupuncture. Second control group included 40 female patients received non-steroid anti-inflammatory drugs and physical electrotherapy.

Results of this study showed high efficacy of medical rehabilitation of cervical vertebral syndromes in the subside illness phase with combined methods of low-frequency magneto-light therapy and various types of acupuncture. Treatment showed full regress of neurological symptoms and improvements in quality of life in the first group in 85% of patients , partial regress in 15%. Second group full regress of symptoms 60%, partial regress – 40%.

Conclusions: Proven high clinical efficacy of low-frequency magneto-light therapy with acupuncture in medical rehabilitation practice of cervical vertebral syndromes in female patients.

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Effect of smoking status on total energy expenditure

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Abstract

Individuals who smoke generally have a lower body mass index (BMI) than nonsmokers. The relative roles of energy expenditure and energy intake in maintaining the lower BMI, however, remain controversial. We tested the hypothesis that current smokers have higher total energy expenditure than never smokers in 308 adults aged 40-69 years old of which 47 were current smokers. Energy expenditure was measured by doubly labeled water during a two week period in which the subjects lived at home and performed their normal activities. Smoking status was determined by questionnaire. There were no significant differences in mean BMI (mean ± SD) between smokers and never smokers for either males (27.8+5.1 kg/m^2 vs. 27.5+4.0 kg/m^2) or females (26.5+5.3 kg/m^2 vs. 28.1+6.6 kg/m^2), although the difference in females was of similar magnitude to previous reports. Similarly, total energy expenditure of male smokers (3069+764 kcal/d) was not significantly different from that of never smokers (2854+468 kcal/d), and that of female smokers (2266+387 kcal/d) was not different from that of never smokers (2330+415 kcal/d). These findings did not change after adjustment for age, fat-free mass and self-reported physical activity. Using doubly labeled water, we found no evidence of increased energy expenditure among smokers, however, it should be noted that BMI differences in this cohort also did not differ by smoking status.

Introduction

Numerous cross-sectional studies have indicated that body mass index (BMI) is lower in cigarette smokers than in nonsmokers [1-3] , and that leanness correlated directly with duration, but not intensity of smoking, with longer duration associated with lower BMI [4-6]. Recent statistical analyses of data sets from both the 2005-2006 National Health and Nutrition Examination Survey (NHANES) [2] and the 2005 National Health Interview Survey [7] confirmed findings from prior studies indicating that smokers weighed significantly less than nonsmokers. Individuals who stop smoking have been reported to gain weight after they quit, and this prospect can discourage tobacco cessation [1,3,6]. Women seem to be somewhat more susceptible to weight gain following smoking cessation than men. In a 10 year study, the mean weight gain attributable to cessation was 5.0 kg in women and 4.4 kg in men [3]. Multiple studies have shown that 33-75% of ex-smokers reported weight gain within the first year of cessation [8].

While the exact cause of this weight gain is unclear, two hypotheses, which are not mutually exclusive, are frequently proposed. The first is that smoking increases energy expenditure due to nicotine's effects in raising metabolic rate, resulting in decreased energy expenditure with cessation [8-10]. In 1986, Hofstetter et al. reported that 24-hour energy expenditure increased in smokers by 140-200 kcal/day on a day with smoking compared to a day without smoking, and no corresponding change in mean basal metabolic rate [11]. Further studies have since yielded conflicting results with most finding an increase in resting metabolic rate (RMR) shortly after nicotine administration. Walker et al. found a 6% increase in RMR after 20 minutes of smoking [12] and Dalloso et al. documented a 3% increase in RMR after smoking a single cigarette [10]. Several studies, however, failed to find a corresponding increase in RMR measured either before or after smoking a single cigarette before they ceased smoking [13,14].

The second hypothesis is that smoking alters energy intake by inducing an anorexic effect [9] and, by extension, smoking cessation leads to weight gain due to increased intake [15]. Findings on this subject vary and results are also inconsistent. In a study by Jessen et al., during a two hour period, nicotine administration was negatively associated with hunger and food consumption and positively associated with satiety [16]. Perkins et al. found increased satiety and lower caloric intakes following nicotine administration [17]. However, in another study, the same authors found higher caloric intakes with nicotine administration [18].

Unfortunately, the second hypothesis is difficult to test because self-report tools were used to measure intake. Numerous studies have shown that self-reported dietary records are prone to error, usually in the direction of underreporting [19]. In addition, the first hypothesis has historically been difficult to test, with the exception of short-term measurements of RMR over a period of minutes or hours. This is because measuring total energy expenditure (TEE) under free-living conditions was difficult in the past [20]. This has changed, however, with the development of the doubly labeled water (DLW) method for measuring TEE [21]. This method is based on the observation that after a loading dose of water labeled with deuterium and ^{18}O, the deuterium is eliminated from the body as water, while the ^{18}O is eliminated as water and carbon dioxide. The difference between the elimination rates is therefore proportional to carbon dioxide production and hence energy expenditure [21]. The doubly labeled water technique provides a measure of TEE which includes RMR, thermic effects of meals (TEM) and physical activity energy expenditure (PAEE). Moreover, the DLW method averages TEE over a period of days to two weeks thus providing a counterpart to energy intake in assessing contributions to energy balance [21].

Utilizing DLW, Warwick and Baines reported no difference in energy expenditure between smokers and non-smokers. This study, however, included only 11 smokers and 10 nonsmokers and thus had limited power [22]. We calculate the standard error for the difference in TEE between smokers and nonsmokers in the study of Warwick and Barns to be

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249 kcal/d and thus the smallest difference they could have expected to identify ($P < 0.05$) with 80% power would have been nearly 700 kcal/d.

We analyzed data from the National Cancer Institute's (NCI) Observing Protein and Energy Nutrition (OPEN) Study, which was conducted to assess the structure of measurement error in self-reported dietary assessment instruments. In OPEN, TEE was measured by DLW in 484 adults [23,24]. Each participant also reported their smoking status, thus providing an opportunity to test the hypothesis that the TEE of smokers is greater than that of never-smokers.

Methods

Subjects

Of the original 484 adults (age 40-69 years) who participated in the OPEN study, which was conducted during 1999, 10 were excluded because they lacked smoking data, 150 were excluded because they had smoked at one time, but were currently non-smokers, and 33 were excluded because of missing energy expenditure data [23]. The remaining 304 participants (158 male, 146 female), 47 of which (20 male, 27 female) were current smokers were included in the analysis. The majority of the participants in OPEN were white males and females with some college education or higher [25]. The study was approved by the institutions involved and participants provided signed informed consent.

Study Design

The OPEN Study evaluated the structure of dietary measurement error in food frequency questionnaires (FFQs) and 24-hour dietary recalls (24 HRs) by using DLW and urinary nitrogen as biomarkers of TEE and protein. Full details can be found elsewhere, including dietary data [25,26]. In brief, a randomized sample of 5,000 individuals aged 40-69 years of age within the Washington DC area was contacted via telephone. After an initial telephone encounter, participants meeting inclusion criteria were invited to a series of 3 clinic visits. DLW studies were performed between the first visit and second visit (11-14 days later).

DLW studies were performed using a five-urine-specimen protocol. DLW was administered orally at the first visit at a dose of 2 g of 10 atom percent ^{18}O labeled water and 0.12 g of 99.9 atom percent ^{2}H labeled water per kilogram of estimated total body water along with a 50-ml rinse of the dose bottle. Urine specimens were then collected at 2, 3, and 4 hours after the dose with the 2 hour specimen being discarded. Urine was again collected twice approximately 14 days later. TEE was calculated with the modified Weir equation, assuming a respiratory quotient of 0.86. Isotope analysis was performed as previously described [25].

Participants reported their smoking status and physical activity level on questionnaires. Smoking status was based on the number of cigarettes smoked during the lifetime. Those who had smoked less than 100 cigarettes in their lifetime were classified as never-smokers and those who had smoked more than 100 cigarettes were classified as smokers. Those who reported quitting smoking were classified as past smokers and those who did not report quitting were classified as current smokers. Only never smokers and current smokers were included in the study. The DLW method thus provided a measure of total daily energy expenditure averaged over a period 11 to 14 days during which there were no restrictions or instructions regarding smoking.

Physical activity was assessed with the OPEN Study Physical Activity Questionnaire, the same questionnaire that was used in NHANES 2001-2002 [27]. Participants reported the duration and frequency of specific domains of physical activity, which were translated into MET-minutes of physical activity per week.

The FFQ utilized in the OPEN study was the Diet History Questionnaire (DHQ) (available at http://www.riskfactor.cancer.gov/DHQ/ webcite), developed and evaluated at NCI [25]. This questionnaire assessed the frequency of intake for 124 individual foods/food group items during the preceding 12 months and evaluated the portion size of most items. Data from the DHQ was analyzed by Diet*Calc Software (version 1.4.3, 2005, National Cancer Institute, Bethesda, MD).

The 24 HR used in the OPEN Study was a standardized five-pass method, developed by the US Department of Agriculture for use in national dietary surveillance [26].

Fat free mass (FFM) was calculated indirectly based on TBW from the deuterium and O18 dilution spaces and body mass.

Statistical Analysis

All statistical analyses were performed using SAS (version 9.13, SAS Institute, Inc, Cary NC). Male and female participants were analyzed separately using a T-test to assess smoking-group differences for continuous outcomes. Multiple regression models were fitted to compare the TEE of current smokers to never smokers including four variables significantly influencing TEE: gender, age (years), fat free mass (FFM) (kg), and physical activity (PA) (MET minutes/week). Least-squares (LS) means were also calculated and compared between smokers and non-smokers. All regression analyses were performed using the PROC GLM procedure in SAS. An

Table 1. Subject Characteristics

	Males		Females	
	Smokers (n = 20)	Never-Smokers (n = 138)	Smokers (n = 27)	Never-Smokers (n = 119)
Age (y)	50.6 ± 8.7	53.4 ± 8.3	53.6 ± 8.1	52.2 ± 7.9
Height (cm)	177.4 ± 7.7	176.3 ± 7.9	164.6 ± 6.6	162.3 ± 6.7
Weight (kg)	87.7 ± 18.9	85.4 ± 13.9	71.8 ± 16	74.1 ± 18.3
BMI (kg/m^2)	27.8 ± 5.1	27.5 ± 4.0	26.5 ± 5.3	28.1 ± 6.6
FFM (kg)	60 ± 11.4	58 ± 7.9	42.8 ± 7.1	42.4 ± 6.7
Physical Activity (MET min/wk)	1128 ± 1154	1558 ± 1411	1467 ± 1679	1516 ± 1387

Values are written as mean ± standard deviation. FFM = Fat Free Mass.

Table2. TEE in smokers and non-smokers

	Overall	Never smokers	Current smokers	Difference
Males	2882 ± 518	2854 ± 468	3069 ± 764	214 (p = 0.08)
Females	2319 ± 409	2330 ± 415	2266 ± 387	64 (p = 0.46)

Values are written as mean +/- standard deviation in kcal/day. The number of subjects is the same as in Table 1.

Table 3. Pearson's correlation between TEE and related factors

Factor	Correlation coefficient (r)	p-value
Females		
FFM (kg)	0.75	p < 0.001
Age (y)	-0.34	p < 0.001
SR PA (MET*h)	0.13	p = 0.13
Males		
FFM (kg)	0.76	p < 0.001
Age (y)	-0.21	p = 0.001
SR PA (MET*h)	0.12	p = 0.16

The number of subjects is the same as in Table 1. SR PA = Self reported physical activity in mets/hour.

Table 4. Comparison of total energy expenditure (kcal/d) by smoking status in males and females after controlling for the effects of age, fat-free mass, and self-reported physical activity.

	Never smokers	Current Smokers	Difference
Males			
Adjusted for age and FFM	2870+28	2961+72	91 (p = 0.24)
Adjusted age, FFM, and SR PA	2867+27	2979+71	111 (p = 0.15)
Females			
Adjusted age and FFM	2334+24	2252+51	-81 (p = 0.16)
Adjusted for age, FFM, and SR PA	2334+24	2252+51	-81 (p = 0.15)

*Values are given as least square mean +/- standard error of the mean. Age in years, FFM = fat-free mass in kg, and SR PA is self reported physical activity in mets*hour. The number of subjects is the same as in table 1.*

Table 5. Multiple Regression Coefficients for Factors Related to Total Energy Expenditure

	Coefficient estimation	p-value
Males		
Smoking	111.9	p = 0.15
FFM	43.6	p < 0.001
Age	-13.3	p < 0.001
SR PA	0.05	p = 0.006
Females		
Smoking	-81.8	p = 0.15
FFM	45.0	p < 0.001
Age	-3.5	p = 0.21
SR PA	0.01	p = 0.40

FFEM = Fat free mass. SR PA = Self reported physical activity.

α value of < 0.05 was considered statistically significant.

Results

Subject characteristics are shown in Table 1. Among both males and females, no significant differences were detected between smokers and non-smokers for age, height, weight, BMI, FFM, or reported PA. Consistent with other studies, the female participants, on average, expended less energy than the males (2319 +/- 409 kcal/day vs. 2882 +/- 518 kcal/day, p < 0.001, Table 2). When categorized by smoking status, unadjusted TEE in female smokers and never smokers averaged 2266 ± 387 kcal/day and 2330 ± 415 kcal/day respectively and was not significantly different (p = 0.46). Among males, unadjusted average TEE was 3069+764 kcal/d in smokers and 2854+468 kcal/d in never smokers, also not significantly different (p = 0.08).

FFM and age were significantly correlated with TEE in both genders (Table 3). The effect of smoking status on TEE is shown in Table 4. No difference in least-square means was found.

Table 5 shows the multiple regression coefficients for several factors related to TEE. Smoking was not significantly associated with TEE in either males or females. FFM was the strongest factor positively associated with TEE in both males and females, while age and PA were positively associated in males, but not in females.

Discussion

This is the largest study to compare total energy expenditure

between free-living smokers and never-smokers using DLW. In so doing, we greatly strengthen the findings of Warwick and Baines, who also reported no difference in energy expenditure between smokers and non-smokers (2877+/- 496 kcal/d vs. 2541 +/- 628 kcal/d), by including 47 smokers and 257 non-smokers compared to their small sample of 11 and 10 smokers and non-smokers [22]. Our larger sample, therefore, allowed us to detect a difference of 216 kcal/d compared with 700 kcal/d for the smaller study. Based on the unadjusted TEE value, the 95% CL for the TEE difference between male smokers and never smokers was -28 to 458 kcal/d and among females the 95% CL of the difference was -237 to 109 kcal/d. TEE, however, was strongly correlated with FFM and thus should be adjusted for FFM as well as age [23]. After adjustment, the 95% CL for TEE in male and female smokers compared to never smokers was -64 to 246 kcal/d and -193 to 29 kcal/d, respectively.

Other investigators have compared the energy requirements of smokers and non-smokers using dietary records with mixed results [28-35]. Such conflicting findings are not surprising in light of data showing that many individuals under-report their dietary energy intake by amounts often in excess of 15% indicating that the use of self-reported energy intake as a proxy measure of energy expenditure can be problematic [24,36]. In contrast, the DLW method has been carefully validated against measured TEE in a metabolic chamber and shown to be accurate within 1-2% with a coefficient of variation of 4-7% [37].

Our finding of no significant difference in the TEE between current smokers and never smokers appears inconsistent with previous studies indicating that the RMR component of TEE is higher in smokers than non-smokers. For example, following multiple administrations of two nicotine doses to eighteen male smokers, Perkins et al. found that RMR acutely increases 3% above placebo after both moderate and low doses [38]. Likewise, Dallosso and James found that metabolic levels were elevated by 2.8% and 1.5%, 1-30 and 31-60 min after smoking [10]. This increase appears to be acute rather than long-term. No animal studies have found a significant increase in long-term RMR after frequent exposure to cigarette smoke or nicotine [39,40]. Similarly, most human studies found that smoking has insignificant long-term effects on RMR [13,14,40].

Unfortunately, RMR was not measured in the OPEN Study and thus we cannot direct compare results with regard to RMR. We can, however, calculate the effect of a short-term post-smoking percentage change in RMR to TEE. Assuming that smoking causes a 3 to 5% increase in RMR for up to 1 h after smoking, we would predict that a person who smokes a pack a day of cigarettes would have an increase in TEE of 30 to 50 kcal/day. This small change is inside the confidence interval for our results in males and too small to detect. In females, however, we can reject the hypothesis that smoking causes a 30-50 kcal/d higher TEE in females. It should be noted, however, that our results are not necessarily inconsistent with a small increase in RMR. If one assumes that smoking is primarily a sedentary activity, then it is possible that the time spent smoking leads to reductions in physical activity that may compensate any potential increase in RMR associated with smoking. To test for this possibility, we also adjusted TEE for self-reported physical activity, but that adjustment had no influence on the results. Self-reported physical activity, however, is also subject to reporting error and thus our conclusion regarding this hypothesis is weak [41].

One limitation of the DLW technique is that it measures CO_2 production and inhaled cigarette smoke contains CO_2 produced from the burning of the tobacco [38]. Thus CO_2 that is absorbed by the body will result in an inherent overestimation of energy expenditure in the DLW based measurement. Assuming that the consumed portion of each cigarette contains 0.7 g of combustible material and that the smoker inhales two-thirds of the CO_2 produced by the cigarette, smoking two packs a day would produce an error of about 0.6 mol of CO_2 per day or 2-4% of true CO_2 production. Thus, heavy smoking is expected to result in an overestimate of CO_2 production and therefore energy expenditure [38]. This limitation of the DLW method, however, does not alter our conclusion that smoking does not increase energy expenditure compared to never smokers, as correction for inhaled CO_2 would act to further reduce the TEE of our smokers by 45 to 115 kcal/day.

A second limitation of this analysis is that the OPEN cohort is not a representative sample. In particular, the male participants, who were classified as current smokers, did not have numerically lower BMIs than nonsmokers. This atypical BMI pattern may be due to behavioral differences between OPEN participants and that of other studies as the OPEN cohort was highly educated, (83% with one year of college or more including 32% with post-graduate education), from the same geographic area (Bethesda, MD and surrounding communities) and likely had a high level of health consciousness related to volunteer bias. Thus it is possible that the OPEN current smokers may have smoked less than participants in other studies resulting in the atypical BMI pattern seen in males

While it is true that dietary reporting may be associated with under eating [42] , this is only true for food records as subjects know they are being observed. The OPEN study, however, utilized FFQs and 24-hour dietary recalls. FFQs ask about intake the past year while recalls are unannounced and ask about intake "yesterday." Both may be subject to error and bias but not to under eating. Under eating, if it did exist, would have an effect on caloric intake but very minimal effect on total energy expenditure which is the endpoint of our study.

Our findings among female participants, however, are more typical in that the BMIs of current smokers were 1.6 kg/m^2 less than those of never smokers. The adjusted TEE was not only not greater than that of never smokers, but actually trended toward a lower value than those of never smokers ($p = 0.15$) and thus did not support a hypothesis that TEE is elevated in smokers.

Our TEE findings among the participants from the OPEN study do not support the hypothesis that smoking increases TEE. These findings differ from those found in NHANES in which clear differences in BMIs between smokers and nonsmokers were shown. Also, although this is the largest reported cohort of smokers who have TEE data as measured by the DLW method, the total number of current smokers was still only 47 individuals, thus power was limited.

These indicate that weight gain following smoking cessation is a result of increased caloric consumption versus decreased

TEE, indicating that health practitioners should include dietary counseling in smoking cessation programs with an eye toward decreasing post-cessation weight gain.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DPB drafted the manuscript. RPT, AFS and AS were involved in the conception of the study, conception and conduct of the OPEN Study, data interpretation, and manuscript preparation; DAS was involved in the conception of the study, analysis of doubly labeled water data, data interpretation, and manuscript preparation. ZZ and LAJ were involved in analysis of doubly labeled water data and data interpretation. All authors read and approved the final manuscript.

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Bedeutung von Wachstumsfaktoren für die Behandlung von chronischen Wunden am Beispiel des diabetischen Fußulcus

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Zusammenfassung

Einleitung

Ulcera in Folge von Diabetes mellitus sind aufgrund der zunehmenden Prävalenz der Erkrankung ein schwerwiegendes Problem mit einem großen Anteil an der weltweiten Krankheitslast. Aufgrund langer Krankenhausaufenthalte, Rehabilitation, häufig erforderlicher häuslicher Betreuung und Inanspruchnahme sozialer Dienstleistungen sind diabetische Fußkomplikationen auch teuer. Eine Therapie mit Wachstumsfaktoren könnte eine wirksame innovative Wundbehandlung zusätzlich zu einer Standardwundversorgung darstellen.

Forschungsfragen

Wie ist der Nutzen einer Therapie mit Wachstumsfaktoren allein oder in Kombination mit anderen Technologien zur Behandlung des diabetischen Fußulcus unter medizinischen, ökonomischen, sozial-ethischen und juristischen Aspekten zu beurteilen?

Methodik

In relevanten Datenbanken wird eine systematische Literaturrecherche nach englisch- und deutschsprachigen Publikationen seit 1990 durchgeführt. Kostenwerte werden an das Preisniveau von 2008 angepasst und in Euro umgerechnet. Die Überprüfung und Bewertung der methodischen Qualität der medizinischen und ökonomischen Studien erfolgt anhand von anerkannten methodischen Standards der evidenzbasierten Medizin und der Gesundheitsökonomie.

Ergebnisse

Es können insgesamt 25 Studien identifiziert werden (14 randomisierte kontrollierte Studien (RCT), neun Kosten-Effektivitäts-Analysen und zwei Metaanalysen.

In den 14 RCT wird eine zur Standardwundversorgung adjunkte Therapie mit der Standardwundversorgung/Placebo oder einer extrazellulären Wundmatrix verglichen: in sechs Studien Becaplermin, in zwei Studien der rekombinante humane epidermale Wachstumsfaktor (rhEGF), in einer Studie der basische Fibroblastenwachstumsfaktor (bFGF) und in fünf Studien die biologisch aktiven Hautimplantate Dermagraft und Apligraf. Die Studiendauern liegen bei zwölf bis 20 Wochen. Die Studienpopulationen umfassen insgesamt von 17 bis zu 382 Patienten, im Durchschnitt 130.

Für eine Behandlung mit Becaplermin, dem Wachstumsfaktor rhEGF und mit den Hautimplantaten Dermagraft und Apligraf zeigt sich im Vergleich zu einer Standardwundversorgung allein in jeweils acht von 13 Studien ein Vorteil hinsichtlich einer vollständigen Wundheilung und der Dauer bis zu einer vollständigen Wundheilung mit statistisch signifikanten Unterschieden. Ein Nachweis für den Nutzen einer Behandlung mit bFGF kann nicht erbracht werden. Die Rate unerwünschter Ereignisse beträgt in vier der 14 Studien mehr als 30% je Studienarm, ist jedoch zwischen den Studiengruppen nicht unterschiedlich. Die methodische Qualität der Studien ist mit deutlichen Mängeln behaftet.

Becaplermin kann als kosteneffektiv betrachtet werden. Divergierende Kostengrundlagen und inkrementelle Kosten-Effektivitäts-Relationen lassen eine eindeutige Aussage zu Dermagraft und Apligraf nicht zu.

Diskussion

Unterschiede in der Standardwundversorgung erschweren den Vergleich der Studienergebnisse miteinander. Vor dem Hintergrund kleiner bis sehr kleiner Studienpopulationen und einer mit deutlichen Mängeln behafteten methodischen Qualität der Studien mit hohem Verzerrungspotential sind

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die Ergebnisse zur Effektivität und Kosten-Effektivität nur eingeschränkt aussagekräftig. Die Studiendauern und weitere Follow-up-Phasen sind für eine Überprüfung der Nachhaltigkeit der Interventionen und Beobachtung von Ulcusrezidiven oder unerwünschten Ereignisse infolge der Behandlung wie z.B. der Entwicklung maligner Tumoren zu kurz.

Schlussfolgerung/Empfehlungen

Hinweise auf den Vorteil einer adjunkten Therapie mit Wachstumsfaktoren bei diabetischen Ulcera für eine vollständige Wundheilung und die Dauer bis zu einer vollständigen Wundheilung sind gegeben. Zusätzliche methodisch hochwertige Studien mit adäquaten Fallzahlen und ausreichend langen Nachbeobachtungsphasen sind notwendig, in denen neben klinisch relevanten Zielgrößen auch weitere patientenrelevante Parameter wie z.B. die gesundheitsbezogene Lebensqualität, Akzeptanz und Toleranz der Behandlung untersucht werden.

Schlüsselwörter: Randomisierung, Übersichtsliteratur, Diabetes mellitus, Diabetes mellitus, Typ 1, Diabetes mellitus, Typ I, Diabetes mellitus, Typ II, Diabetes mellitus, Typ 2, diabetischer Fuß, diabetesbezogene Komplikationen, Wundheilung, kontrollierte klinische Versuche, randomisierte, rekombinante Proteine, plättchenaktivierender Faktor, thrombozytogener Wachstumsfaktor, Wachstumsfaktor, Therapie mit Wachstumsfaktoren, Diabetes, Fußulcus, Wundbehandlung, Wundversorgung, Wundversorgung in der Pflege, Wundversorgung bei Diabetes, Wundenmanagement, Infektionsschutz, diabetischer Ulcus, diabetischer Fußulcus, Podologie, chronische Wunde, schwer heilende Wunde, Pflege, interdisziplinäres Team, systematische Übersicht, Übersichtsarbeit, Effektivität, Wirksamkeit, Kosten-Effektivität, Kosteneffektivität, HTA, Health Technology Assessment, Gesundheitsökonomie

Kurzfassung

Einleitung

Chronische Wunden stellen ein schwerwiegendes medizinisches und gesellschaftliches Problem dar. Für die Medizin und Pflege besteht die Herausforderung in der Versorgung der Patienten, die über Monate und zum Teil auch Jahre behandelt werden müssen, was hohe volkswirtschaftliche Kosten nach sich zieht.

Für die Patienten bedeuten chronische Wunden durch Schmerzen und Immobilität eine erhebliche Einschränkung der Lebensqualität. Im Weiteren kann das auch zu sozialer Isolation und finanziellen Problemen führen.

Das Wundmanagement stellt aufgrund dieser psychosozialen Belastung und dem Auftreten heterogener Begleiterkrankungen eine große Herausforderung für das Gesundheitswesen eines Landes dar. Neben der medizinischen Versorgung durch verschiedene Fachärzte spielt die häusliche Pflege der Patienten eine zentrale Rolle.

Eine Wundform ist das diabetische Fußulcus, das aufgrund der zunehmenden Prävalenz der Erkrankung ein schwerwiegendes Problem mit einem großen Anteil an der weltweiten Krankheitslast ist. 2 bis 10% aller Menschen mit Diabetes mellitus leiden an einem Fußulcus und die Neuerkrankungsrate liegt jährlich bei 2,2 bis 5,9%. Aufgrund langer Krankenhausaufenthalte, Rehabilitation, häufig erforderlicher häuslicher Betreuung und Inanspruchnahme sozialer Dienstleistungen sind diabetische Fußkomplikationen auch teuer.

Eine Therapie mit Wachstumsfaktoren könnte eine wirksame innovative Wundbehandlung zusätzlich zu einer Standardwundversorgung darstellen.

In Deutschland zugelassen ist der Wirkstoff Becaplermin, der unter dem Handelsnamen Regranex vertrieben wird, und durch opportunistische Verkäufe ist auch eine Therapie mit dem biologisch aktiven Hautimplantat Apligraf möglich.

Forschungsfragen

Medizinische Forschungsfragen

- Wie wirksam und sicher ist der Einsatz von Wachstumsfaktoren allein zur Behandlung des diabetischen Fußulcus im Vergleich zu anderen Technologien?
- Wie wirksam und sicher ist der Einsatz von Wachstumsfaktoren in Kombination mit anderen Technologien zur Behandlung des diabetischen Fußulcus im Vergleich zu anderen Technologien?

Ökonomische Forschungsfragen

- Wie ist die Kosten-Effektivität von Wachstumsfaktoren allein zur Behandlung des diabetischen Fußulcus im Vergleich zu anderen Technologien?
- Wie ist die Kosten-Effektivität von Wachstumsfaktoren in Kombination mit anderen Technologien zur Behandlung des diabetischen Fußulcus im Vergleich zu anderen Technologien?

Ethisch-soziale und juristische Forschungsfragen

Welche ethisch-sozialen und juristischen Aspekte fließen in die Bewertung einer Behandlung des diabetischen Fußulcus mit Wachstumsfaktoren ein?

Methodik

In den Datenbanken MEDLINE, EMBASE, AMED, BIOSIS Previews, MEDIKAT, Cochrane Library – Central, gms, SOMED, CAB Abstracts+CAB, ISTPB+ISTP/ISSHP, ETHMED, GLOBAL Health, Deutsches Ärzteblatt, EMBASE Alert, SciSearch, CCMed, Social SciSearch, Karger-Verlagsdatenbank, Kluwer-Verlagsdatenbank, Springer-Verlagsdatenbank, Springer-Verlagsdatenbank PrePrint, Thieme-Verlagsdatenbank, Derwent Drug File, IPA, gms Meetings, DIQ-Literatur, HECLINET, Hogrefe-Verlagsdatenbank und Volltexte, Thieme-Verlagsdatenbank PrePrint, Krause & Pachernegg Verlagsdatenbank wird eine systematische Literaturrecherche nach englisch- und deutschsprachigen Publikationen seit 1990 durchgeführt. Speziell nach HTA-Berichten (HTA = Health Technology Assessment), systematischen Reviews und gesundheitsökonomischen Evaluationen wird in den Datenbanken der Cochrane-Library CDSR, NHS-CRD-DARE, der International Agency for Health Technology Assessment NHS-CRD-HTA, des National Health Service in Großbritannien NHSEED und der HTA-Datenbank der Deutschen Agentur für Health Technology Assessment) gesucht.

Die identifizierte Literatur wird von zwei unabhängigen Gutachtern hinsichtlich der Thematik und der festgelegten Ein- und Ausschlusskriterien überprüft. Eingeschlossen werden Studien zur Wirksamkeit und Sicherheit von Therapien mit Wachstumsfaktoren bei Patienten mit diabetischen Ulcera. Zur Beantwortung der ökonomischen Fragestellungen werden vollständige ökonomische Evaluationen herangezogen. Zur Vergleichbarkeit der

Ergebnisse der internationalen Studien werden die Kostenwerte an das Preisniveau von 2008 angepasst und in Euro umgerechnet. Die Überprüfung und Bewertung der methodischen Qualität der eingeschlossenen medizinischen und ökonomischen Studien erfolgt anhand von anerkannten methodischen Standards der evidenzbasierten Medizin.

Ergebnisse

Es können insgesamt 25 Studien identifiziert werden, die die Ein- und Ausschlusskriterien erfüllen. Darunter fallen 14 randomisierte kontrollierte Studien (RCT) zur medizinischen Evaluation, neun Kosten-Effektivitäts-Analysen zur ökonomischen Evaluation und zwei Metaanalysen.

In fünf der 14 RCT wird eine zur Standardwundversorgung adjunkte Therapie durch den Wirkstoff Becaplermin in verschiedenen Konzentrationen mit einer Standardwundversorgung verglichen. In einer Studie wird der Vergleich einer Konzentration Becaplermin mit einer extrazellulären Wundmatrix untersucht und in zwei Studien der Wirkstoff rhEGF in verschiedenen Konzentrationen mit Placebo. Das Wachstumsfaktoren sezernierende Hautimplantat Dermagraft und eine Standardwundversorgung werden in vier Studien mit einer Standardwundversorgung verglichen sowie in einer weiteren Studie das Wachstumsfaktoren sezernierende Hautimplantat Apligraf und eine Standardwundversorgung mit einer Standardwundversorgung allein. Die Studiendauer liegt bei zwölf bis 20 Wochen. Die Studienpopulationen umfassen insgesamt von 17 bis zu 382 Patienten, durchschnittlich 130, im Median 90 Patienten.

Für den Vergleich von Becaplermin mit einer Standardwundversorgung zeigt sich hinsichtlich des Anteils von Patienten mit einer vollständigen Wundheilung ein Vorteil mit statistisch signifikanten Unterschieden zugunsten von Becaplermin, mit einer größeren Evidenz durch mehr Studien für die Konzentration von 0,01% als für die Konzentration 0,003%. Auch die Dauer bis zu einer vollständigen Wundheilung ist für Patienten mit einer Becaplerminbehandlung mit statistisch signifikantem Gruppenunterschied deutlich kürzer. Im Vergleich von Becaplermin mit der Wundmatrix OASIS zeigte sich im Anteil von Patienten mit einer vollständigen Wundheilung und der Dauer bis zu einer vollständigen Wundheilung ein Trend zum Nachteil von Becaplermin, der allerdings keine statistische Signifikanz erreichte.

Die Behandlung mit dem rekombinanten humanen epidermalen Wachstumsfaktor (rhEGF) in den Konzentrationen von 0,04% und 0,015% bewirkt im Vergleich zu einer Standardwundversorgung eine kürzere Dauer bis zu einer vollständigen Wundheilung, und in der Konzentration von 0,015% zeigt die Therapie auch Vorteile hinsichtlich des Anteils von Patienten mit einer vollständigen Wundheilung, alle Gruppenunterschiede sind statistisch signifikant. Ein Nachweis für den Nutzen einer Behandlung mit dem Wachstumsfaktor bFGF kann nicht erbracht werden.

Eine ein Mal wöchentliche Applikation des biologisch aktiven Hautimplantats Dermagraft über acht Wochen ist im Vergleich zu einer Standardwundversorgung sowohl hinsichtlich des Anteils von Patienten mit einer vollständigen Wundheilung als auch in der Dauer bis zu einer vollständigen Wundheilung vorteilhaft mit statistisch signifikanten Gruppenunterschieden. Letztere können für die Therapie mit dem biologisch aktiven Hautimplantat Apligraf verglichen mit einer Standardwundversorgung nur in Bezug auf den Anteil von Patienten mit einer vollständigen Wundheilung und zugunsten des Implantats festgestellt werden. Die Rate unerwünschter Ereignisse beträgt in vier der 14 Studien mehr als 30% je Studienarm, ist jedoch zwischen den Studiengruppen nicht unterschiedlich. Die methodische Qualität der Studien ist mit deutlichen Mängeln durch fehlende Verblindung, unklare Angaben zum Concealment und fehlende Beschreibung des Randomisierungsverfahren s und der Intention-to-treat- (ITT)-Methode behaftet.

Die Ergebnisse der Kosten-Effektivitäts-Analysen der neun gesundheitsökonomischen Evaluationen zeigen, dass Becaplermin als kosteneffektiv angesehen werden kann und dass divergierende Kostengrundlagen und inkrementelle Kosten-Effektivitäts-Relationen eine eindeutige Aussage zu Dermagraft und Apligraf unmöglich machen. Je nach Publikation ist bei beiden Präparaten entweder von einer Kosten-Effektivität auszugehen oder von einer für den Entscheidungsträger problematischen Relation.

Unter bestimmten Voraussetzungen ist Becaplermin in Deutschland erstattungsfähig. In seiner Arzneimittelrichtlinie legt der Gemeinsame Bundesausschuss fest, dass die Verwendung von Becaplermin nur zweckmäßig ist„wenn die Therapie diabetischer, neuropathischer Ulcera mit intensiver adäquater Wundbehandlung einschließlich ständiger Druckentlastung erfolglos geblieben ist.“ Becaplermin ist damit nur dann Therapie der Wahl, wenn andere Verfahren fehlgeschlagen sind. Apligraf ist nur in der Schweiz und den USA zugelassen, doch es gibt über opportunistische Verkäufe nach Deutschland einen Zugang zu der Therapie.

Diskussion

Vor dem Hintergrund der überwiegend kleinen bis sehr kleinen Studienpopulationen und einer mangelhaften methodischen Qualität der Studien mit hohem Verzerrungspotential sind die Ergebnisse nur eingeschränkt aussagekräftig.

Darüber hinaus erschweren Unterschiede in der Standardwundversorgung, durch verschiedene chirurgische Verfahren, unterschiedliche Häufigkeiten erneut erfolgender Debridements während des Studienverlaufs und die jeweilige Erfahrung der behandelnden Ärzte mit schwer heilenden Wunden die Vergleichbarkeit der Studien miteinander. Weitere Variationen liegen in unterschiedlichen Methoden zur Druckentlastung, zur Wundversorgung und Strenge der Infektionskontrolle zwischen Kliniken, Ärzten und Pflegepersonal.

Die Studiendauern von maximal 20 Wochen und weiteren Follow-up-Phasen in nur vier Studien sind für eine Überprüfung der Nachhaltigkeit der Interventionen und Beobachtung von Ulcusrezidiven oder unerwünschten Ereignisse infolge der Behandlung wie z.B. Entwicklung maligner Tumoren zu kurz.

Trotz dieser geringen Studiendauern erweist sich eine Behandlung mit Becaplermin in den Modellierungen durchgehend als kosteneffektiv mit entweder geringen zusätzlichen Kosten je Effektmaß oder sogar Kostenersparnissen. Zur Kosten-Effektivität einer Behandlung mit Dermagraft lassen sich aufgrund der vorliegenden Publikationen sehr schwer Aussagen treffen, denn schon die Angaben aus den beiden Publikationen für die zugrunde

gelegten Kosten für ein Stück Dermagraft differieren. Auch eine klare Aussage über die Kosten-Effektivität von Apligraf ist nicht zu machen, denn die Ergebnisse der beiden Studien sind widersprüchlich.

Schlussfolgerung/Empfehlungen

Hinweise auf den Vorteil einer adjunkten Therapie mit Wachstumsfaktoren bei diabetischen Ulcera für eine vollständige Wundheilung und die Dauer bis zu einer vollständigen Wundheilung sind gegeben.

Die Prävention und Behandlung diabetischer Ulcera ist äußerst komplex. Viele Faktoren tragen zu ihrer Entwicklung bei und müssen bei der Wahl der Behandlung berücksichtigt werden.

Für Kliniker, die diese Wahl treffen müssen, ist die aktuelle Evidenzlage nicht zufriedenstellend, denn allein schon die Empfehlungen, was eine Standardwundversorgung umfassen sollte, differieren. Für alternative Wundbehandlungsmethoden ist die Evidenzlage für Empfehlungen noch schwächer.

Methodisch hochwertige Studien zur Behandlung diabetischer Ulcera mit Wachstumsfaktoren allein oder in Kombination mit anderen Technologien mit adäquaten Fallzahlen sind infolgedessen notwendig, denn angesichts des demographischen Wandels und der wachsenden Prävalenz von an Diabetes mellitus Erkrankten wird auch die Prävalenz diabetischer Ulcera steigen.

Zusätzlich zur Beobachtung klinisch relevanter Zielgrößen sollten in zukünftigen Studien die patientenrelevanten Parameter gesundheitsbezogene Lebensqualität, Akzeptanz, Zufriedenheit, Compliance und Toleranz der Behandlung untersucht werden, sowie auch weitere Stratifizierungen der Studienpopulationen vorgenommen werden wie beispielsweise eine nach Diabetestyp oder Ulcuslokalisation getrennte Untersuchung.

Vitamin D - das neue Multitalent

Anselm Budweg

Rachitis und Lebertran, Osteoporose und Calcium mit Vitamin D machten für den Laien und die behandelnde Ärzte seit 50 Jahren das Vitamin D zum Vitamin für gesunde Knochen.

Erst seit knapp 10 Jahren erwachte neues Interesse am Vitamin D. Man entdeckte viele neue hochinteressante evolutionsbiologische, epidemiologische und funktionsbiologische Zusammenhänge. So etwa sind die durch die westliche Welt laufenden Grippewellen überwiegend zurückzuführen auf den schweren Vitamin D Mangel von Dezember bis Februar. Ursächlich ist der im Winter nördlich des 40 Breitengrades auftretendene Lichtmangel.

Das Auffinden von Vitamin D-Rezeptoren in fast allen Organen deckt plötzlich die Zusammenhänge auf zwischen Vitamin D Mangel und Tumorerkrankungen, Autoimmunerkrankungen, Herzerkrankungen, Darmerkrankungen und vieles andere mehr.

Die offiziell empfohlenen Tagesdosierungen von 200 IE (= 5 µg) Vitamin D sind im Licht dieser neuen Befunde extrem unterdosiert.

Um die international empfohlenen Blutspiegelkonzentrationen von ca 30-70 ng/ml (= 50 -170 mmol/l) sind Tageszufuhren oral oder über Sonnenlicht in der Haut gebildet von mindestens 1000 - 2000 IE (teilweise noch höher) Vitamin D (teilweise noch höher) erforderlich. Beim Gesunden sind keine Nebenwirkungen bei einer langfristigen täglichen Zufuhr von unter 10000 IE Vitamin D zu erwarten.

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iASPP is over-expressed in human non-small cell lung cancer and regulates the proliferation of lung cancer cells through a p53 associated pathway

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Abstract

Background

iASPP is a key inhibitor of tumour suppressor p53 and is found to be up-regulated in certain malignant conditions. The present study investigated the expression of iASPP in clinical lung cancer, a leading cancer type in the world, and the biological impact of this molecule on lung cancer cells.

Methods

iASPP protein levels in lung cancer tissues were evaluated using an immunohistochemical method. In vitro, iASPP gene expression was suppressed with a lentvirus-mediated shRNA method and the biological impact after knocking down iASSP on lung cancer cell lines was investigated in connection with the p53 expression status.

Results

We showed here that the expression of iASPP was significantly higher in lung cancer tissues compared with the adjacent normal tissues. iASPP shRNA treatment resulted in a down-regulation of iASPP in lung cancer cells. There was a subsequent reduction of cell proliferation of the two lung tumour cell lines A459 and 95D both of which had wild-type p53 expression. In contrast, reduction of iASPP in H1229 cells, a cell with little p53 expression, had no impact on its growth rate.

Conclusions

iASPP regulates the proliferation and motility of lung cancer cells. This effect is intimately associated with the p53 pathway. Together with the pattern of the over-expression in clinical lung cancers, it is concluded that iASPP plays an pivotal role in the progression of lung cancer and is a potential target for lung cancer therapy.

Background

The tumour suppressor protein p53 is a transcription factor that responds to oncogenic stress such as DNA damage, oncogene activtaion, γ-irradiation and certain chemotherapeutic drugs that may result in apoptosis and cell-cycle arrest [1,2]. In over half of all of human cancers, p53 has been shown to be either lost or mutated. In those tumours in which the p53gene is intact, the regulation of the p53 pathway may be defect [3,4]. The type of response following p53 activation depends upon a number of factors. Importantly, oncogenic transformation can cause a switch in the cell's response to p53 activation from growth arrest to programmed cell death. As a result, tumour cells are more likely to undergo apoptosis following p53 activation than the corresponding normal cells, making the p53 pathway an excellent target for therapeutic intervention [5-8].

iSAPP, Inhibitory Member of the ASPP (Apoptosis-stimulating protein of p53) family is also known as the Rela-associated inhibitor, RAI and NF-kappa-B-interacting protein-1, NKIP1. It is one of the conserved inhibitors of p53. The discovery of the ASPP family of proteins as specific regulators of p53 identifies a new mechanism by which the apoptotic function of p53 is regulated [9,10]. The name of the family is based on the domain organization of the proteins (ankyrin repeat, SH3, and proline-rich domain containing protein) as well as their functions (apoptosis-stimulating protein of p53) [11]. There are three family members in humans: ASPP1, ASPP2, and iASPP. ASPP1 and ASPP2 enhance the apoptotic function of p53, whereas iASPP inhibits p53-dependent apoptosis [9-13]. Regulatory function of p53 by iASPP is conserved from worm to human [14]. The expression levels of ASPP proteins in human malignancies have been sparsely reported. While ASPP1 and ASPP2 are down-regulated in a large percentage of tumours, iASPP has been found to be significantly higher in patients with acute leukaemia when compared with healthy donors or patients with leukaemia but with complete remission. iASPP has also been found to be over-expressed in breast carcinomas [14-19]. There has been no reports on the expression of the ASPP family and their possible functions in lung cancer.

In the present study, we first investigated the protein expression of iASPP in human lung cancer tissues and further evaluated the impact of knocking down iASPP, by way of lentivirus shRNA to iASPP, on the function of a panel of lung cancer cell lines which exhibited different p53 expression pattern.

Methods

Cell lines, reagents and antibodies

Human lung cancer cell lines A549, 95D and H1229 were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured either in in F-12K medium (A549 cells) or RPMI-1640 medium (95D cells and H1229 cells) containing 10% fetal bovine serum, at 37°C with 5% v/v CO2. MTT assay reagents were purchased from DingGuo Biotech (Beijing, China). 5-Bromo-2'-deoxyuridine (BrdU) assay reagents were purchased from Chemicon International (Temecula, CA, USA). Anti-iASPP mAb used for Western blot assay was purchased from Abcam (Boston, MA, USA). Anti-iASPP rAb using for Immunohistochemical assay was purchased from Rockland Immunochemicals, Inc., (Gilbertsville, PA, USA). Anti-GAPDH monoclonal was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA).

Lentivirus-mediated shRNA delivery

Sequences of iASPP shRNA were inserted into the pGCL-GFP

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lentivirus RNAi expression system. The shRNA containing vectors were transfected together into 293T cells with pHelper1.0 and the lentiviral helper plasmid pHelper2.0 to generate the respective lentiviruses. Viral stocks were collected from the transduced 293T cells and were used to infect A549 cells, 95D cells and H1229 cells. The sequence of iASPP nonsense shRNA was: AATGTACTGCGCGTGGAGA; the sequence of iASPP shRNA was AACACATGGATCTGAAGCAGA. The mRNA and protein levels were measured 72 hrs after cells being infected.

Quantitative RT-PCR analysis of iASPP expression

Total RNA was extracted and reverse transcribed into cDNA using M-MLV-RTase (Promega, Madison, WI, USA). The resulting cDNA was used for PCR using the SYBR-Green Master PCR Mix (Applied Biosystem, Carlsbad, CA, USA) in triplicates. Primers for qRT-PCR were as follows: iASPP forward primer: GGCGGTGAAGGAGATGAAC; iASPP reverse primer: TGATGAGGAAATCCACGATAGAGA; p53 forward primer: CCTCCTCAGCATCTTATCC; p53 reverse primer: ACAAACACGCACCTCAAA; p21 forward primer: GGGACAGCAGAGGAAGACC; p21 reverse primer: GACTAAGGCAGAAGATGTAGAGC; PUMA forward primer: GACGACCTCAACGCACAG; PUMA reverse primer: CACCTAATTGGGCTCCATCTC. PCR and data collection were performed on the TP800 qPCR System (Takara, Japan). All quantitations were normalized to an endogenous β-actin control. β-actin forward primer: GGCGGCACCACCATGTACCCT; β-actin reverse primer: AGGGGCCGGACTCGTCATACT. The relative quantitation value for each target gene compared to the calibrator for that target is expressed as 2-(Ct-Cc) (Ct and Cc are the mean threshold cycle differences after normalizing to β-actin).

Western blot

Protein samples prepared from the cells were subjected to SDS-PAGE, transferred to PVDF membranes (Millipore, Kankakee, IL, USA) and detected with appropriate primary antibodies followed by horseradish peroxidase-conjugated goat, anti-mouse or rabbit IgG. The protein signals were detected using SuperSignal West Dura Extended Duration Substrate (Pierce, Rockford, IL, USA).

MTT assay

All the cells, including those transfected, were grown in exponential phase and detached by trypsin/EDTA treatment. Viable cells (2,000 cells/ml) were plated into 96-well tissue culture plates (100 µl complete medium/well) and cultured at 37°C in 5% CO2. At different time points, MTT reagent was added (10 µl per well) and incubated at 37°C for 4 hr. The reaction was stopped with addition of 100 µl DMSO and the optical density was determined at OD570 nm on a multi-well plate reader. Data from three independent experiments were analyzed by student t test and $p < 0.05$ was considered statistically significant.

BrdU assay

Cells were seeded into 96-well plates (1,500 cells/well) and cultured at 37°C in 5% CO2. At different time points, BrdU reagent was added (20 µl/well) and incubated at 37°C for 4 hr. Cells were then fixed in a fixation solution for 30 min. After washing three times with a washing buffer, anti-BrdU antibody was added (50 µl/well) and incubated at 37°C for 1 hr. Following washing, an enzyme conjugated secondary antibody was added (50 µl/well) and incubated at 37°C for a further 30 min. Colour was then developed by incubation with 50 µl TMB substrate for 30 min in dark and the optical density was determined at OD490 nm on a multi-well plate reader. Data from three independent experiments were analyzed by student t test and $p < 0.05$ was considered statistically significant.

Colony formation assay

Cells were seeded into six-well plates (200 cells/well) (in three duplicate wells) and cultured at 37°C in 5% CO2. After two weeks, the cells were fixed with paraformaldehyde for 30 min and then stained with GIEMSA for 10 min. ddH2O was used to wash the cells three times to obtain a clean background. The number of colonies and the cell number in each colony were counted and statistically analyzed.

Immunohistochemical Staining

Tissues sections (5-µm thick) were dewaxed, followed by quenching the endogenous peroxidase with 3% H2O2 in methanol for 30 min. Prior to staining, non-specific binding was blocked by incubation with 10% BSA in PBS at 37°C for 1 hr. Tissue sections were incubated with pre-immune IgG or specific antibodies in PBS containing 1% BSA at 4°C overnight, followed by incubation with a horseradish peroxidase-conjugated anti-mouse or rabbit antibody. Colour was then developed by incubation with an ImmunoPure Metal Enhanced Diaminobenzidine (DAB) Substrate kit (Pierce). After each incubation, tissue sections were washed three times in PBS for 10 min. Tissue sections were finally counterstained with hematoxylin. For determination of iASPP immunoreactivity, cytosolic staining of yellowish or brownish granules was graded as follows: 0 for background staining, 1 for faint staining, 2 for moderate staining and 3 for strong staining. In addition, positive staining areas in entire tissue section were graded as follows: 0 for <5%, 1 for 5-25%, 2 for 26-50%, 3 for 51-75%, and 4 for 76%-100%. When combining these two parameters, 0-2 and ≥3 were considered negative and positive staining, respectively.
Statistical analysis was carried using SPSS (version 16). Fisher's Exact test was used for analyzing the immunohistochemical data and Student t test for other quantitative data.

Results

Over-expression of the iASSP protein in human lung

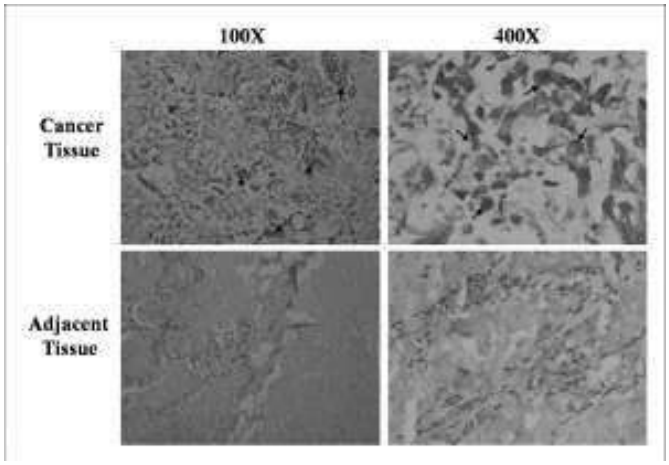

Figure 1. Over-expression of iASPP in human lung cancer. Expression of iASPP in cancer tissue (top panels) and adjacent tissue (low panels). Results are representative of more than ten immunohistochemical staining experiments. Positively stained tumour cells are indicated by arrows.

Table 1. The expression pattern of iASPP in lung cancer samples revealed in immunohistochemistry analysis.

	Cancer tissue		Adjacent tissue	
Staining grade*	Case	Percentage	Case	Percentage
<5%	7	14.29%	30	65.22%
5%-25%	10	20.41%	10	21.74%
26%-50%	12	24.49%	4	8.70%
51%-75%	11	22.45%	2	4.35%
75%-100%	9	18.37%	0	0.00%

** Samples were defined as "iASPP positive" when the proportion of tumor cells positive for iASPP (staining rate) was more than 50%.*

cancer tissues

To determine the expression pattern of iASPP protein in human lung cancer, immunohistochemical analysis was performed on 49 pairs of tumour and normal tissues from patients pathologically verified for having lung carcinoma. Immunoreactivity for iASSP antigens was seen in 40.82% (20/49) of lung cancer tissues and 4.35% (2/46) of adjacent non-cancerous tissues (Figure 1), $p < 0.001$ by Fisher's Exact test. The number of samples that were assigned each score is shown in Table 1. Others previously reported that SNPs in iASPP are related to the response of chemotherapy and radiotherapy in NSCLC (non-small cell lung cancer) patients [20]. Thus, the increase in iASPP expression may play an important role in the pathogenesis of human lung cancer.

Reduction of iASPP mRNA and protein expression by shRNA in vitro

To further investigate the biological role of iASPP in lung cancer cells, we knocked down iASPP transcript in human lung cancer cell lines A549 cells, 95D cells and H1229 cells. This was carried out by employing shRNA technology. shRNA to iASPP was constructed into PGCL-GFP vector using lentivirus transfection system, as shown in Figure 2A. The lentivirus transfection system successfully down-regulated iASPP expression at both mRNA level and protein level in A549 cells, 95D cells and H1229 cells, in comparison with blank controls or nonsense shRNA controls (Figure 2B, C).

iASPP down-regulation inhibited the proliferation of A549 cells and 95D cells

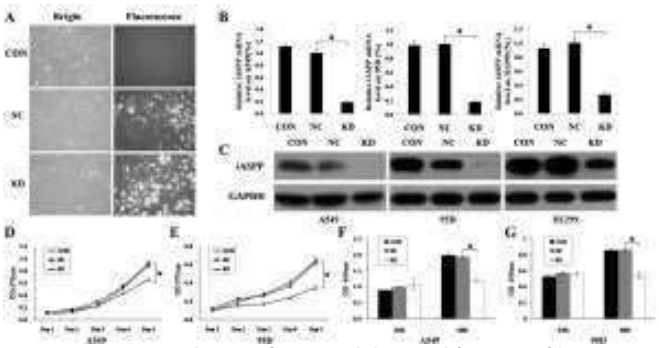

Figure 2. Down-regulation of iASPP inhibits proliferation of lung cancer cells. (A) Pictures for Lentivirus tranfection of blank control (CON), nonsense shRNA (NC) and iASPP shRNA (KD). (B) The iASPP mRNA level was downregulated by iASPP shRNA in A549, 95D and H1299 cells. (C) The iASPP protein level was downregulated by iASPP shRNA in A549, 95D and H1299 cells. (D-E) Proliferation of A549 cells (D) and 95D cells (E) were inhibited when treated with iASPP shRNA by MTT assay. (F-G) Proliferation of A549 cells (F) and 95D cells (G) were inhibited when treated with iASPP shRNA by BrdU assay. CON: blank control; NC, nonsense shRNA; KD: iASPP shRNA. Results represent the mean ± S.D. of three independent experiments.

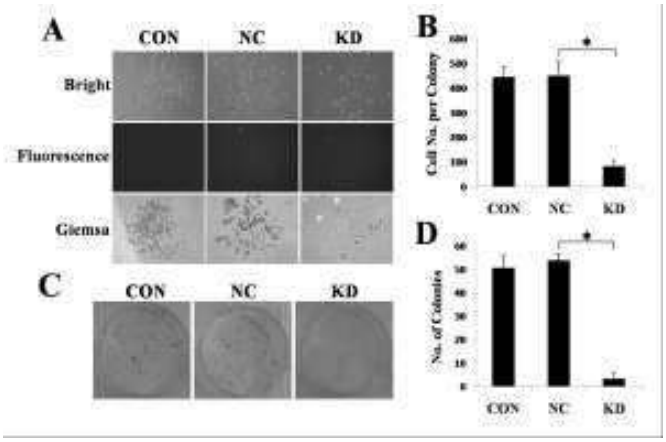

Figure 3. Down-regulation of iASPP inhibits colony formation of lung cancer cells. (A-B) iASPP shRNA (KD) reduced the number of cells in a signal clonal colony compared with the blank control (CON) or nonsense shRNA (KD). (C-D) iASPP shRNA (KD) also reduced the number of cells compared with the blank control (CON) or nonsense shRNA (KD). Results represent the mean ± S.D. of three independent experiments.

Using the iASPP knockdown cells, we first tested the change of cell growth, using the MTT assay. The results showed a significant decrease of cell growth and indicated that cell proliferation was inhibited after transfection with iASPP shRNA both in A549 cells and 95D cells (Figure 2D, E). To further conform this result, we carried out an alternative proliferation assay, the BrdU assay. Consistent with the observations made with the MTT assay, both A549 cells and 95D cells showed lower BrdU positive staining after the cells were treated with iASPP shRNA than the blank controls or cells treated with nonsense shRNA for 48 hours (Figure 2F, G). Our results thus suggested that shRNA mediated down-regulation of iASPP inhibited proliferation of lung cancer cells. It is interesting to observe that BrdU assay appeared to be a more sensitive method than the MTT assay. A significant difference was seen as early as 48 hours with the BrdU assay (Figure 2D), whereas with the MTT assay (Figure 2F), the difference was seen after 4 days.

iASPP down-regulation inhibited the colony formation of A549 cells

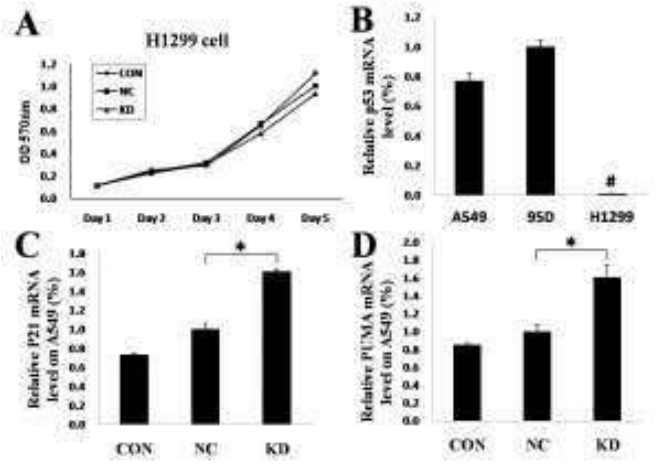

Figure 4. Down-regulation of iASPP inhibits proliferation of lung cancer cells through p53. Down-regulation of iASPP did not affect the proliferation of H1229 cells. (B) A549 cells and 95D cells had high p53 mRNA level, whereas H1299 cells had very low p53 mRNA levels. (C-D) The mRNA level of p21 and PUMA, which was downstream of the p53 pathway, was up-regulated when treated with iASPP shRNA in A549 cells. CON: blank control; NC, nonsense shRNA; KD: iASPP shRNA. Results represent the mean ± S.D. of three independent experiments.

Transfection of A549 cells with iASPP shRNA resulted in a significant decrease in cell numbers in each colony, when compared with A549 cells treated with blank control or nonsense shRNA (Figure 3A, B). The number of colonies with more than 50 cells was also decreased in iASPP shRNA transfected cells (Figure 3C, D). 95D cells were unable to form colonies and were unable to be assessed for this cellular function (data not shown).

iASPP regulated lung cancer cell proliferation, a connection with the p53 pathway

Although iASPP down-regulation inhibited the proliferation of A549 cells and 95D cells, there was no changes in the proliferation of H1229 cells when treated with iASPP shRNA, as evident from both MTT and BrdU assays (Figure 4A, and data not shown). Since iASPP has been reported as a regulator of p53, we thus suspected that the difference between A549/95D cells and H1229 cells in their response to iASPP shRNA may be due to different p53 expression. Consistent with our hypothesis, it was found that the H1229 cells expressed little iASSP mRNA, whereas A549 cells and 95D cells showed high levels of the wild-type iASPP mRNA (Figure 4B). As a downstream effector of p53 activation, p21 and PUMA [21,22] were also found to be significantly increased in A549 cells after treatment with iASPP shRNA, when compared with blank control or nonsense shRNA (Figure 4C, D). This provides further support that iASPP regulates lung cancer cell proliferation in a manner that is associated with the p53 pathway.

Discussion

To the best of our knowledge, the present study is the first report of up-regulation of iASPP in human lung cancers. Our study has shown that there was an over-expression of the iASPP protein in lung tumour tissues in comparison with normal tissues and that knocking down iASPP resulted in an inhibition of cell proliferation. Given the prevalent of lung cancer and the death rate associated with the tumour type [23], our finding has important bearing.

In accordance with our results, others have reported that SNPs in iASPP are associated with response to chemotherapy or combined chemotherapy and radiotherapy in NSCLC (non-small cell lung cancer) patients [20]. Together, it suggests that iASPP plays important roles in lung cancer. In the present study, we also demonstrated that iASPP down-regulation inhibited the proliferation and colony formation of lung cancer cell lines A549 and 95D in vitro. A few recent reports have indicated that iASPP is over-expressed in breast cancers and certain types of leukaemia, and that down-regulation of iASPP could inhibit the proliferation of these cancer cells [14-19]. Together with our results in lung cancer, it is plausible to suggest that iASPP acts as a common factor of regulating the proliferation in difference cancer cells. Over-expression of iASPP may be involved in both the establishment and the progression of tumours, whereas down-regulation of iASPP may inhibit tumour development. In this regard, drugs specifically directed against iASPP could be beneficial in the treatment of cancers, including lung cancer [24].

p53 is perhaps one of the best known tumour suppressor genes and plays a critical role in regulating cell proliferation through induction of growth arrest or apoptosis. iASPP is the most phylogenetically conserved inhibitor of p53 identified thus far. Our results suggesting that iASPP down-regulation in H1229 cells did not affect the proliferation and colony formation is very interesting. H1229 cells have little p53 expression as shown in the literature and in the present study. This thus confirms that the effect of iASPP is largely dependent upon p53 in order to regulate the apoptotic pathway, as seen with other cancer cell types. Besides p53, the p53-related protein p73 also has the similar functions. Previously, iASPP has been shown to form a protein complex with p73 to regulate cell death [8,24]. Whether iASPP forms the same complex with p73 in lung cancer cells deserve further exploration.

The ASPP family consists of three members, ASPP1, ASPP2 and iASPP. All three proteins share sequence similarity at their C-terminus which contains their signature sequences of ankyrin repeats, SH3 domain and Proline-rich region. The C-terminus is the preferred binding site for p53 [25]. In contrast to iASPP, ASPP1 and ASPP2 activate p53 to stimulate specifically the expression of pro-apoptotic target genes. This implies that ASPP1 and ASPP2 can compete with iASPP for binding to p53, thereby inhibiting the ability of iASPP and stimulating the apoptotic function of p53. However, the detailed mechanism requires further exploration.

Conclusions

We report that that iASPP is over-expressed in human non-small cell lung cancer tissues when compared with normal tissues. shRNA mediated down-regulation of iASPP results in inhibition of proliferation and colony formation of two lung tumour cell lines A459 and 95D which have high wild-type p53 expression [26,27] and has no impact on the H1229 cells which has little p53 expression in vitro. This further suggests that iASPP is a target for lung cancer therapy associated with p53 pathway.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JC and FX contributed equally to the study design, experimental work, data analysis and preparation of the manuscript. LZ and WGJ contributed to the study design, data analysis and manuscript preparation. All the authors read and approved the manuscript.

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Possibilities of Human Ecological Medicine in cholelithiasis treatment

Elena V. Donchenko, Alexander A. Zhukov

Key words:

cholelithiasis, chronic cholecystitis, treatment.

The main purpose of this work is to provide with new, broader conception about the reasons and mechanisms of cholelithiasis formation, as well as about possibilities of its non-surgical methods of therapy.

Cholelithiasis disease proceeds with gallstones formation in bile ducts and gallbladder.

At the end of the 20th century there had been registered more than 5 mln. patients in Germany and more than 15 mln. patients in the USA who had suffered from cholelithiasis. It is notable that about 10% of adult population suffers from this disease. According to the medical statistics the number of patients suffering from cholelithiasis disease considerably increases with aging and makes more than 30% by people who have reached 70 years [8]. Today cholecystectomy is considered to be a «gold standard» of cholelithiasis treatment. In many countries the frequency of surgeries on bile ducts has already exceeded the frequency of other abdominal surgeries (including appendectomy). In the seventies there had been

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executed more than 250 thousand of cholecystectomies in the USA, in the eighties – more than 400 thousand, and in the nineties – up to 500 thousand surgery procedures.
Cholecystectomy like the majority of other surgery procedures leads toward a number of postsurgical complications (clinical signs are kept by 15–40% [4] of patients, there appears postcholecystectomic syndrome). Cholecystectomies do not always improve the quality of patients' lives (there can appear repeated attacks of gallstone colic). Moreover, in some cases these surgery procedures do not remove the cause of pathological process.
There were offered other non-surgical methods of cholelithiasis treatment, for example saxifragant solutions intake (chenodeoxycholic acid, ursodeoxycholic acid), or lithotripsy [5,8]. However all these methods do not prevent from disease progression. Besides, the frequency of recurrent gallstones formation, demanding repeated courses of therapy, is rather high when application of those methods.
There is a common view that the etiology of cholelithiasis is not examined good enough. From our point of view direct causes of disease progression include:
• derangement of cholesterol metabolism;
• derangement of mineral metabolism due to lesion of parathyroid glands as a result of autoimmune thyroiditis
• hepatopathy and cholestasis
• biliary dyskinesia
Gallstones form from main components of bile. There exists cholesterol, pigmental, calcareous and mixed stones. Concrements, consisting of only one component, are rather uncommon. Overwhelming majority of gallstones has mixed structure with cholesterol prevalence. They contain 80% of cholesterol, calcium salts and mucin [4,6,8].
It is necessary to focus special attention on gallbladder's functions. According to our point of view its function is more complex and important than many physicians believe. Gallbladder is not simply "an unnecessary sac for stones" that could be easily removed. It solves the important task of secretions outflow from bile ducts. When it stretches after contraction there appears negative pressure that helps to "pump-out" contents from hepatic and bile ducts. All words said above can be confirmed by that fact that during the course of cholelithiasis treatment we observed on control ultrasonic scanning the appearance of new stones in gallbladder, which diameters did not exceed 5mm (more often 1-3mm), against the background of restoration of bile outflow and liver density reduction.
Proceeding from the solid work experience of our clinic, on the basis of clinical observations we formed our own idea about the pathogenesis of disease that icludes:

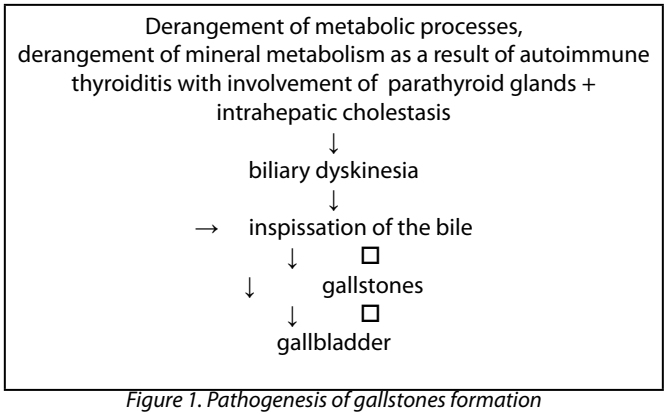

Figure 1. Pathogenesis of gallstones formation

Dr. Elena Donchenko

Ph. d. – the author and the founder of human ecological medicine. Gastroenterologist, therapist, phytotherapist. Clinic of Ecological Medicine Chief Executive. Elena Donchenko has 5 patents on internal diseases treatment methods (including treatment of hepatitises, bronchial asthma, arterial hypertension, organism's detoxication – hyperthermic intestinal dialysis, and in stomatology). She is a laureate of the Robert Koch Medal awarded by European Academy of Natural Sciences for achievements in the sphere of medical science and for the development of ecological technologies in medicine. Donchenko E.V. is the honorary academic of European Academy of Natural Sciences (Germany).

About 2000 patients with leading diagnosis "Cholelithiasis" were treated in our clinic during last 5 years. 34 cases were subjected to statistical processing. All patients were 25-75 years old, at the average 52 - 75 years old. 29% of patients were man and 71% - woman.
We use following methods of investigation: ultrasonic scanning, complete blood count, biochemical blood analysis (lipidogram, SPGT, SGOT, alkaline phosphatase, GGT, bilirubin, ionized Ca+) detection of thyroid antibody titers (anti-thyroglobulin autoantibodies, anti-thyroid peroxidase autoantibodies).
We had developed the unique methods of ultrasonic scanning of gallstones in 3D regime with the help of two sensors. This method allows to estimate the density of concrements according to our own scale, to visualize correlation between dense and soft parts of gallstone, as well as to carry out dynamic observations over the process of lithodialysis (gallstones dissolution).
Treatment was provided on an outpatient basis of Clinic for Ecological Medicine, St. Petersburg, Russian Federation.
Human Ecological Medicine is rather new concept in modern medicine that includes following principals:
• Human organism is a single, integral system that possesses its own mechanisms of self-regulation and auto-reconstitution.
• Disease is an adaptive response of an organism to the disturbed balance.
• Treatment should be focused on providing of assistance to human organism in restoration of disturbed balance, but not on medicamental suppression and blocking of morbid symptoms.
• Person's mental sets, attitudes, self-love and harmony with the environment play great role in the process of rehabilitation.
Principals of rehabilitation:
1. DO NOT PREVENT ORGANISM FROM RESTORATION OF DISTURBED BALANCE (i.e. do not use drugs and methods of treatment, blocking those processes in human organism, which play protective and adaptive role).
2. ASSIST THE ORGANISM TO RESTORE THE DISTURBED BALANCE (i.e. restore internal environment, providing it with nutrients, vitamins, microelements, biologically active substances, necessary for realization of native restoration program).
Proceeding from the comprehension of aetiology and pathogenesis of the process of gallstones formation described

above, we can say that cholecystectomy is not only a senseless surgical procedure (it allows to remove only "visible" gallstones, and leaves the source of their formation inside the liver), but also very harmful one, as in future there will occur difficulties with drainage of intrahepatic bile ducts and aggravation of cholestasis.

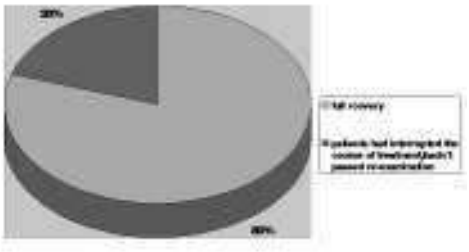

Diagram 1. Number of patients who had taken full course of treatment

Principals of therapy:

1. Endoecological rehabilitation
2. Diet
3. Water schedule
4. Liver functions normalization
5. Mineral metabolism restoration
6. Regular bile outflow support
7. Homeopathy, herbal therapy, enzymotherapy
8. Physical therapy, hirudotherapy
9. Peptide therapy

Treatment methods

A number of unique original solutions (patent №2078555), developed by Elena V. Donchenko – the head of the Clinic for Ecological Medicine – forms the basis of treatment methods.

Endoecological rehabilitation includes:

- Hyperthermic intestinal dialysis
- Intravenous injections of sodium thiosulfate
- Visceral massage
- Hyperthermic intestinal dialysis ©

Mechanism of action:

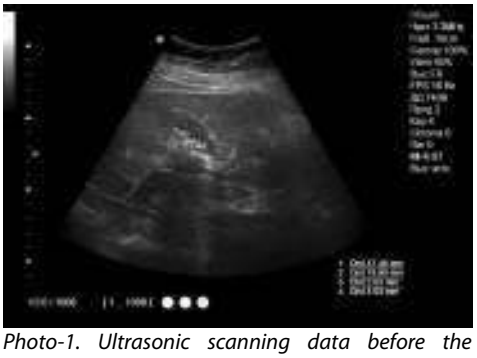

Photo-1. Ultrasonic scanning data before the initiation of treatment

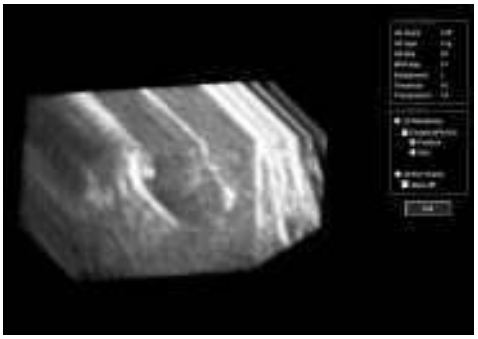

Photo-2 Comcrement's view according to the data of 3D scanning

• Introduction of hot teas (medicinal herbal teas) via intestinal, that is equivalent to intravenous injections;
• Elimination of products of pathometabolism, endo- and exotoxins;
• Stimulation of immune system;
• Dilution of thick secretions of liver and pancreas due to increase of water in bile.
- Intravenous injections of sodium thiosulfate – binding and elimination of toxins; renewal of cell receptor system; simulation of interferon synthesis; antioxidant effect; antihypoxant effect; desensitization; correction of autoimmune response.

Photo-3. Ultrasonic scanning data two months after initiation of treatment

- Visceral massage according to Old Russian technique – pain syndrome relief; elimination of congestions in liver and pancreas; intestinal peristalsis stimulation and detoxication; stimulation of blood and lymph circulation in viscera.
- Peptide therapy (VitOrgan)
• Normalization of gallbladder functions – NeyDIL No 53 (Revitorgan Nr.53)
- Hepatotropic preparations – NeyFegan No 26 (NeyFegan), NeyDIL No 1 (Revitorgan Nr.1)
- Restoration of immune system work - NeyNormin No 65 (NeyNormin)
• Microcirculation improvement - Fega Coren No 61 (Fega Coren)
• Gallbladder mobility normalization – NeyDIL No 3 (Revitorgan Nr.3), NeyDIL No 4 (Revitorgan Nr.4)
• NeyTabs Hepaticum, NeyTabs Cholium, NeyTabs Poly

Therapy results

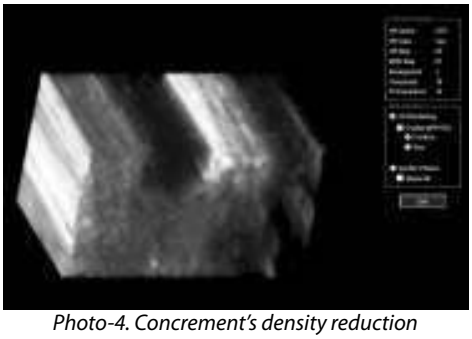

Photo-4. Concrement's density reduction

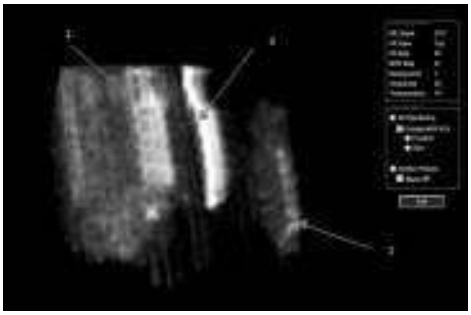

Photo-5. Picture of lithodialysis (gallstones dissolution)

Patients feel themselves better on the 1-3 week of treatment. Painful sensations abate or even disappear, as well as the feeling of heaviness in the right hypochondrium. Biochemical blood values normalize in a month or two. Dynamic of lithodialysis can be clearly observed on ultrasonic scanning.

Period of full lithodialysis varies, depending on a number of factors, including the quantity, size and chemical composition of gallstones, disease duration, adherence to prescriptions and recommendations, provided by attending medical doctor, etc. and can last from 6-8 months up to 1-2 years. In the long-term (6-8-15 years after provided treatment) we can observe the picture of full recovery, absence of any complaints and restoration

of liver and gallbladder's functions according to the results of laboratory and instrumental analysis.
Course of treatment helps to achieve:
- pain syndrome relief
- disappearance of uncomfortable feelings in abdominal cavity and cholestasis
- stool normalization
- improvement of hepatic metabolism and bile outflow
- balancing adjustment of immune system
- restoration of mineral metabolism
- lithodialysis

Observed effects

During the treatment we observe certain staging of process of stones dissolution: on the first stage there occurs stone "swelling". Linear dimensions and volume of stone increase while its density reduces. Then dimensions of stone decrease, its shapes become eroded and rough. 3D regime scanning shows the change in correlation between dense and soft components of stone in favor of more dense one in connection with gradual erosion and dissolution of soft cholesterol layer. Meanwhile dissolution of cholesterol and calcific layers runs simultaneously, that is testified by roughness and disunity of shapes and thickness of dense part. Finally cholesterol component of the stone takes the form of bile clots and gradually eliminates gallbladder in this condition, mixing and dissolving in bile. Dense part of the stone turns into "sand" and also eliminates with bile flow.
Medical case: Patient C. 32 years old had complained on constant dull pain in epigastrium and hypochondrium, intensified after the meal, as well as on heartburn and feeling of abdominal heaviness, also appeared after the meal.
From past history: Patient is suffering from chronic gastroduodenitis, chronic tonsillitis, chronic maxillary sinusitis and periodical herpetic eruptions on lips.

Diagnosis: cholelithiasis, chronic cholecystitis, chronic pancreatitis and autoimmune thyroiditis.
According to the ultrasonic data – gallbladder has dimensions 55x27x27mm, wall up to 3mm. There are a lot of small stones of round shape with dimensions from 2x1mm up to 8x6mm in cavity according to the data of standard ultrasonic scanning in B-regime (see photo 1). From 3D-regime ultrasonic scanning we can clearly identify heterogeneity of stones structure: about 15% of echo structure is represented by hyperechoic (more dense) layer; about 85% of echo structure is represented by the layer of lower echogenicity (see photo 2).
Pains in epigastrium and hypochondrium, as well as feeling of abdomen heaviness and heartburn disappeared in 3-4 weeks after initiation of treatment.
Control ultrasonic scanning carried out two months later had shown some reduction of gallbladder's volume (from 22cm^3 to 14,6cm^3), and total concrements' volume reduction (from 5,4cm^3 to 2,32cm^3).(See photo 3, photo 4)
During the process of lithodialysis we can observe concrement's "exfoliation". The shapes of stones and calcium layer becomes rough and scalloped (see photo 5 – 1-concrement, 2-gallbladder's wall, 3- "notched" calcium layer
The patient continues her treatment. She is undergoing a course of complex therapy. Case monitoring is provided.

Conclusions

Broader approach toward the understanding of process of gallstones formation allows us to think that cholelithiasis is the state of human organism, resulted from derangements of mineral metabolism, processes of bilification and bile outflow, often accompanied by autoimmune thyroiditis, which lead to formation and growth of gallstones, rather than a disease. Using complex approach and original methods of treatment we can achieve the restoration of normal functioning and interaction of internals, full lithodialysis and prolonged relapse-free period.

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Regenerative cryotherapy according to Dorochov® for snoring, tonsillitis, pharyngitis, rhinitis and other diseases stimulation of the immune system

Sergey Dorochov[1], Jürgen Aschoff[2]

Classification. Cryotherapy can be classified on the basis of its clinical effect and as a function of the temperature parameters which affect the impact of the cold factor on tissue.
Cryotherapy: 1. Regenerative, 2. Destructive, 3. Cryosurgery (exstirpative cryotherapy)
Regenerative Cryotherapy according to Dorochov® consists of the brief administration of dosed cold treatment to tissues and organs at temperatures close to the cold-resistance threshold of the tissue. The aim of this type of cryotherapy is to bring about regeneration and functional reactivation at the treatment site. Regenerative cryotherapy causes a reaction in the organism which is linked to local tissue irritation and manifests itself in an elimination of the pathogenic factors, regeneration of tissue, and restoration of functional competence. Monitoring of the cooling parameters in the tissues is a very important point during regenerative cryotherapy since the therapeutic effect is directly linked to these parameters.
Treatment of diseases / complaints in my practice (www.kryopraxis.de) with Regenerative Cryotherapy:
- Snoring and Sleep Apnoea
- Chronic Tonsillitis and chronic pharyngitis
- Chronic Rhinitis of Vasomotor and Atrophic Origin

Regenerative Cryotherapy according to Dorochov is an effective treatment method via which a stable
therapeutic effect can be achieved. It can be employed to:
1. stop snoring and sleep apnoea
2. restore nasal breathing
3. reinstate the protective function of the lymphoid tissue in the tonsils and Waldeyer's throat ring
4. stimulate immune processes
5. eradicate chronic foci of infection in the tonsils, pharynx and nose, thereby preventing complications or sequelae of these infections. These include systemic and rheumatoid diseases of the heart (i.e. endo-, myo- and pericarditis), the blood vessels (e.g. vasculitis), the joints (e.g. polyarthritis), the kidneys (e.g. glomerulonephritis), the internal and external sex organs (e.g. disturbances of potency), the nervous system (e.g. chorea) and the skin (e.g. scleroderma, psoriasis, pustulosis and lupus erythematosus), infectious allergic diseases (e.g. bronchial asthma, atopic and allergic dermatitis, etc.) and immunodeficiency disorders.


Dr. Segey Dorochov

If everyone (but especially children) would undergo prophylactic treatment of the lymphoid tissue of the tonsils, pharynx and nasal mucosa using the method of regenerative cryotherapy, we would observe the following positive effects (especially in children):
- improvement of the protective functions of the organism
- stimulation of the immune system.

We can assume, moreover, that the general risk of contracting systemic, rheumatoid, infectious allergic and oncological diseases, immune deficiency states, snoring and sleep apnoea syndrome - would be distinctly reduced.
Monitoring of the cooling parameters is an important point to be observed during regenerative cryotherapy since achievement of the desired therapeutic effect depends directly on these parameters. On the basis of my extensive experience with cryotherapy, I have designed and patented (German Patent Office in Munich 1993) a mobile cryotherapy unit suitable for use in medical practices. With the aid of this unit, it is possible to keep tissue cooling under control, especially in the ears, nose and throat regions.
With its regenerative effects, cryotherapy opens up vistas for an alternative direction in medicine, namely regenerative medicine.

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Peculiarities of multiple sclerosis in childhood

Vladimir Efimenko

There has been conducted prospective clinical examination of clinical course peculiarities, diagnostics and prognosis of children's disseminated sclerosis over the last 15 years.

Object of study.

31 children with positive multiple sclerosis according to the criteria of Ch. Poser (1983) and co-authors and McDonald and co-authors (2001) (19 girls and 12 boys) were under our observation.

Methods of research.

There have been applied clinical, laboratory, biochemical and immunological researches of blood and spinal fluid, magnetic-resonance tomography of brain and spinal marrow and also visual evoked potentials for presentation of "chess pattern". Follow-up terms amounted from 2 till 15 years.

Received Results

Onset of disease age amounted from 4 till 15 years. There has been observed monosymptomatic debut predominance (67,7% of cases) over polysymptomatic (32,3%). Among initial manifestations the most frequent were: retrobulbar neuritis of optic nerve (22,5%), cerebellar ataxia (9,7%), neuropathy of facial nerve (9,7%), isolated sensitivity and movement functions disorders (6,5% each) etc. At the initial stages remitting clinical course prevailed. Primary and progressive clinical course was established in one case only. In the exacerbation periods pyramid and atactic syndromes dominated. Brainstem affection syndromes dominated by 7 children. Spasticity and pelvic organs disorders were not typical. At the initial stages neurologic symptomatic of exacerbations has been arrested very quickly with the help of pulse therapy, corticosteroids with good dysfunctions recovery. Typical changes and "niduses' spread in space" (according to McDonald et al., 2001) were registered only in 58% of cases by the MRT-research at the debut stage. There has been detected MRT-positive cases increase up to 87% by further observation. In connection with this visual generated potentials' changes had additional diagnostic meaning. Long dynamic follow-up has shown that by 2/3 of patients there had been stable remission reached under the influence of treatment. At the same time by 1/3 of patients there has been transformation into secondary-progressive course with disability signs increase. In these group 3 children aged from 3 years old to 15 years old showed clinical course with rapid progression of neurologic symptomatic (Marburg type).

Prof. Vladimir N. Efimenko

Conclusions

Thus, conducted researches have shown that children's multiple sclerosis has definite peculiarities of debut and course. It is necessary to consider this for neurologists, dealing with children's multiple sclerosis, in their practical work. Received results mean a lot for reasoning of preventive immunotherapy (betaferon, copacson etc.) prescription for children with multiple sclerosis.

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Diagnostic studies of Qigong training effect on personal self-perfection and emotional burnout syndrome

Elena Filimonova

In 1970s the concept of "emotional burnout syndrome" was introduced. This phenomenon occurs to specialists for whom working with people is profession-specific but they don't like it.

Several decades ago Kristina Maslach formulated the phenomenon in the following way: "Burnout is payment for

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sympathy". Consequently, it was recommended not to lay on oneself a burden of other people's problems, not to dissolve in another person's self, pay more attention to one's inner life, not to become a slave to one's duties, to avoid monotony in every possible way, not to try to escape from problems at work and, finally (this last piece of advice is absolutely indisputable), one should simply have one's sleep out. This leads to regular fits of irritation and simultaneously feverish attempts to avoid burnout with the help of quasi-saving methods. Such a person rushes from one extreme to another, often turning to various psychics and "magicians", looking for any way to relieve the stress available. Quite often all this just aggravates the problem.

Within the limits of the research we checked the supposition that doing Qigong leads to positive changes in psychoemotional regulation and axiological and rational sphere of personality.

The following results may serve as illustration of the conclusions about personal correction and self-correction program efficiency.

We studied an emotional component of subjective well-being (according to subjective well-being scale) before and after the experiment and we have got facts about positive changes in respondents' assessment of their own emotional state.

At the initial stage:

• 19,4% of the respondents felt temperate emotional comfort, were quite self-confident, active, able to control their behaviour in an appropriate way and to interact with other people successfully;

• 3,2 % of the respondents were subject to depression and anxiety, pessimism, insularity, it was hard to them to endure stress situations.

At the final stage:

• 45,2% of the respondents felt temperate emotional comfort;

• 0% of the respondents were prone to depression and anxiety.

Elena P. Filimonova
senior research associate

According to the research results, subjective happiness is mostly affected with satisfaction with oneself, with one's way of living and one's family – they are expressed with medium satisfaction level, while level of satisfaction with health and society is much lower. We suppose that there must be direct interconnection between objective environment and subjective happiness.

According to results of research concerning intrapersonal proneness to conflict by method of E.B. Fantalova, 80,4% of the respondents showed signs of intrapersonal conflict at the initial stage.

These are respondents who have high level of discrepancy between concepts of "value" and "accessibility". Principal life values attractive to them are not accessible to them and vice versa the most accessible values are perceived by them as unattractive.

The highest level of discrepancy makes up 66 and 67 points. In case of these respondents, "Values" and "Accessibility" indices are in inverse proportion to each other. This means that everything that is desirable to this respondent is to the same extent inaccessible to him/her. And vice versa: everything that is accessible to him/her is of no value, not wanted, unnecessary, sometimes even irritating and creating subjective "internal ballast".

The lowest result levels - 18 and 21 points. Everything that is of value for these respondents is accessible to them, while everything they have at their disposal is of value to them.

The biggest discrepancy between importance and accessibility has been identified in the following values: active life, health, beauty of nature and art, wealth, happy family life.

Life values like health, wealth, happy family life are important but not accessible to the respondents, and this is inner conflict within the bounds of the above-listed concepts.

At the final stage:

In 52,6% cases intrapersonal conflict has been detected;

In 45,2 % cases integral indicator "Value - Accessibility" has come down;

In 35,5% cases the integral indicator has grown;

In 19,3% cases the integral indicator has remained at the same level.

Research of motivational personality structures before and after the sessions allows to conclude about favourable action of Qigong on the character and intensity of inner conflicts as well as on self-actualization of the respondents (See fig. 1).

Processing and analysis of the research results by method of V.V. Boyko (Appendix 3) gave an opportunity to assess the emotional "burnout" level of the respondents, presence of guiding symptoms of "burnout", to determine to which stress formation phase the dominant symptoms belong and which phase contains the majority of them.

At the initial stage:

Were fully developed:

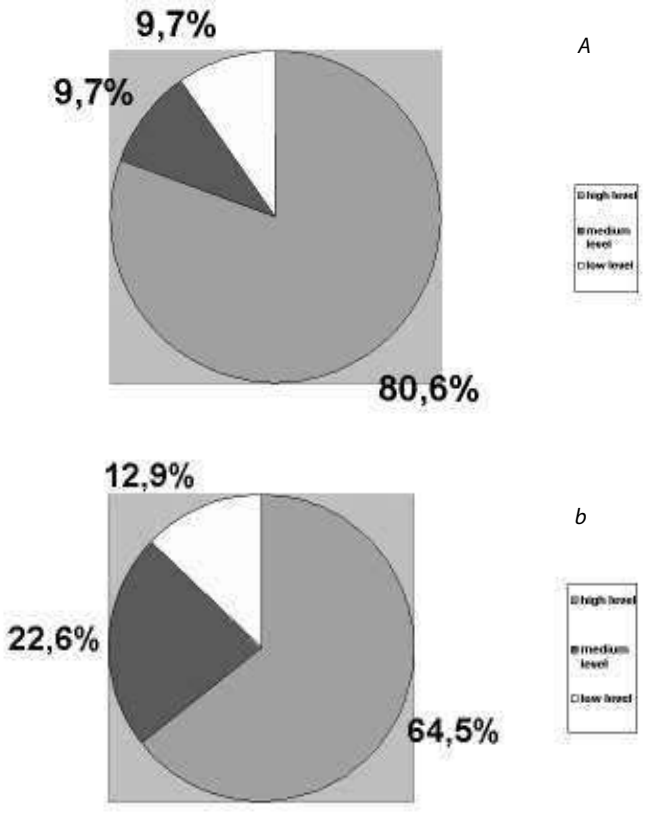

Figure 1. Indicators of discrepancy between «Value» and «Accessibility» at the initial (a) and final (b) stages.

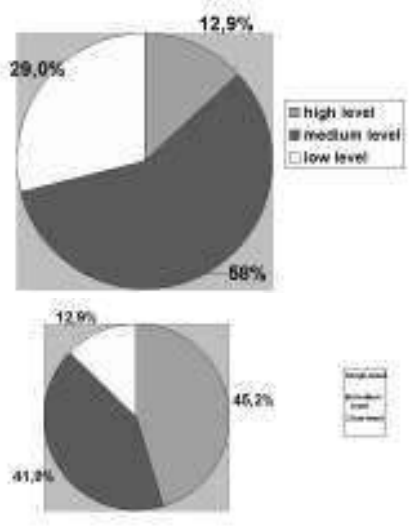

Figure 2. Summary indicator of "emotional burnout" syndrome at the initial (a) and final (b) stages.

- phase of tension – 26% of the respondents;
- phase of resistance – 42% of the respondents;
- phase of exhaustion – 6,7% of the respondents.

Were not developed:
- phase of tension – 45% of the respondents;
- phase of resistance – 13% of the respondents;
- phase of exhaustion – 61,3% of the respondents.

The dominant symptoms are:
In the phase of tension – experiencing psycho-traumatic circumstances (52% of the respondents), alarm and depression (24% of the respondents).
In the phase of resistance – inadequate selective emotional reaction (70% of the respondents), reduction of professional duties (48% of the respondents).
In the phase of exhaustion – personal aloofness (46% of the respondents), emotional deficit (32% of the respondents).
At the final stage:
Fully developed:
- phase of tension – 25,7% of the respondents;
- phase of resistance – 42% of the respondents;
- phase of exhaustion – 6% of the respondents.

Not developed:
- phase of tension – 61,3% of the respondents;
- phase of resistance – 16% of the respondents;
- phase of exhaustion - 71% of the respondents.

Analysis of the summary indicator of "emotional burnout" syndrome allows to conclude about positive effect of following Qigong system on development of the respondents' emotional burnout as psychological defense (see fig. 2).
At the final stage of Qigong sessions the summary indicator of "emotional burnout" syndrome has declined in 65% of cases, has grown in 29% of cases, has remained the same in 6% of cases.
The findings allow to make a conclusion that psychoemotional regulation and axiological and rational sphere of personality during Qigong sessions tend to improve.
Using such a method of self-education and self-perfection one can master the art of one's spiritual and physical potential management as well as contribute to its growth, prevent and overcome one's intrapersonal conflicts.
These findings are not just interesting scientific information, this is the key to self-regulation for each of us.

Psychological correction programme according to Qigong system as personality self-perfection factor

Elena Filimonova

In Qigong system psychological correction of a personality as an independent discipline and as art of healing has formed only in recent decades, from practical application to scientific research and explanation of the method itself.
To a certain extent, this is a dialectical method. A dialogue between two participants. Firstly, this is the philosophy and methods of traditional oriental culture (Chinese). Secondly, methodological scientific research of Qigong systems of the Western culture. Consequently, psychological correction program according to Qigong system as self-perfection factor consists of the following parts.
The principal initial part of respiratory gymnastics according to Qigong system is getting into a tranquil state. This is ability to concentrate without switching over to any outside objects. At this moment cerebral cortex is neither excited nor inhibited; this condition cannot be attained in one day. This is a result of a long training.
At the root of the action mechanism, just like in autogenic training, lies psychoemotional influence on cerebrum cortex functions and subcortex vegetal centres functions.
Attention focusing on one "object" allows cerebral cortex to move away from constant chaos of thoughts and take a rest, at the same time this is no sleepy state but a wakeful one.
For the brain this is kind of gymnastics which trains and strengthens the organism and regulates its activity at the same time. Thus, everything that is good for the central nervous system has a positive impact on the whole organism.
The second key factor of Qigong therapy is breath. From physical viewpoint it positively influences functional systems and gives a massage to thoracic organs and abdominal cavity organs.
By regulating inhalation and exhalation, breath-holding

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and corresponding movements of diaphragm and abdominoanterior wall muscles one can change various parameters of respiratory and cardiovascular system, for example, minute volume of blood. Blood and lymph circulation improve as well as gastrointestinal tract activity, urogenital and endocrine system activity.

Head, neck, mucous tunics of the respiratory tract, larynx, trachea, bronchial tubes and lungs are channels of continuous communication between the environment and nervous system together with the internals which are embryogenetically connected to the principal neuroendocrine structures. These parts are innervated with mixed cerebral nerves and rami of the upper cervical sympathetic ganglion which are formations of the ocular plate cephalic part. The ocular plate is genetically connected with the adrenal medulla and the nerve tube. This means that any impact on arms, face, larynx, trachea, bronchial tubes and lungs entails changes in organs and systems embryogenetically connected with them. These changes can be either positive or negative depending on the character of impact.

The third principal part of Qigong therapy is the movement. It implies physical movements of the whole body, massage and pronouncing sounds. Exercises for arms and legs are of interest because their distal parts, that is hands and feet, have projection areas of the organism as a whole and each organ in particular. (Bergson, 1972, G. Zakharyin and H. Head (end of 19th century), etc.)

In the process of certain exercises the above mentioned zones (according to G. Zakharyin and H. Head) on arms and legs get irritated which produces therapeutic and preventive effect on human organism and psyche. This phenomenon has been explained by modern physiology. Sensory motor functions of the hand and foot occupy significant space in the cerebral cortex, more space than other body parts; this is especially true about the hand whose motor functions occupy more space in the cortex than those of the trunk. The reason for this is that the hand makes an enormous quantity of complicated and manifold movements which play an important role in life of a human being.

Any bodily exercises cause certain energy expenditure to which the organism responds with metabolism acceleration, heartbeat rate growth and breath acceleration. One feels nervous fever, active perspiration and physical fatigue.

While doing Qigong, one experiences preservation and accumulation, one absorbs energy from outside. Metabolism slows down in an optimal way, heartbeat rate and breathing rate decrease. Internals start working in a more synchronous way, in an energy saving mode, energy exchange with the environment gets harmonized. From biochemical viewpoint, the organism sets itself on the optimal mode of endocrine and immune systems activity. These findings are not just interesting scientific information, this is the key to self-regulation for each of us.

31 adults from 25 to 60 years old who do Qigong were subjected to the empiric study. Among them there were 20 females and 11 males. 22 of them have university degree, 10 have got trade education, 3 secondary school education. All of them took part in the experimental study on their own initiative. To get empirical evidence the following methods were used: observation, inquiry, interview, conversation and psychognostic methods.

Empiric study was conducted in two stages: the first stage was forming the group of participants for Qigong program.

The second stage – intense sessions for program participants with a teacher two times a week and on their own every day for 1,5 months. At the end of the program within the limits of the control study another diagnostic testing was organized.

The study was based on individual and group testing: within the bounds of a certain method the responders were given a special form accompanied with application instructions.

The study has shown that psychological state of a person can influence significantly his/her immune system. It means that a person's mental condition, his/her world perception, friendly or angry mood can affect in one or another way his/her hormone or immune system. Just like psychic stress influences negatively work of these systems (the longer the exposure to the influence, the higher the probability of psychosomatic diseases – from cardiovascular to dermatological – including diabetes), Qigong – relaxation, calm deep breathing – can improve the balance between the sympathetic nervous system and parasympathetic one, reduces nervous irritability. Consequently, immune system will work more efficiently, endocrine system will function more steadily, thus, psychosomatic diseases will be prevented.

Qigong psychological correction as a personality perfection factor is based on Qigong's positive regulatory effect on cerebral cortex and subcortex vegetal centres – endocrine, immune, respiratory, urogenital systems of the human organism.

To put it shortly: Qigong respiratory gymnastics allows to take under control different functions of the organism and maintain them on a high level of functionality.

These findings are not just interesting scientific information, this is the key to self-regulation for each of us.

Inkontinenz. Neuro - Geriatrische Probleme

Wolfgang Fischer

Epidemiologische Daten:

- Prävalenz bei >65- jährigen in Industrieländern:
- Zwischen 5% - 30% mit altersabhängig stark zunehmender Tendenz
- Frauen : Männer = 2 : 1
- In Heimen 38 - 87% inkontinente Bewohner !

„Altersbedingte" Ursachen der Inkontinenz

„Auch die Harnblase bekommt Falten"

- physiolog. degenerativer Alterungsprozeß
- Struktur und Abstände der Muskelzellen untereinander ändern sich
- Folge ist Änderung des interstitiellen Ionenmilieus ;
- Dadurch wird die mechanische Reizübertragung durch elektrische Kurzschlußverbindungen überlagert.

Lokale Folge: myogene Detrusrhyperaktivität mit Instabilität
Pathoanatomisch: Degeneration, Separation und Isolation der einzelnen Muskelzellen = wide spread degeneration sowie Kollageneinlagerung im Interstitium= Fibroelastose
Funktionelle Folge:

- Detrusorkontraktilität
- Restharn
- auch ohne Blasenauslaßobstruktion

Krankheitsbedingte Ursachen der Inkontinenz

1. Enthemmte Blase (Verlust der corticalen Hemmung, Detrusorhyperreflexie)

Sy: Dranginkontinenz Imp. Harndrang Kein Restharn	Urs.: zerebrale Ischämie, Blutung zerebrales Trauma MS NPH Stirnhirnsyndrom Mantelkantensyndrom

Typ. Inkontinenzform des höheren Lebensalters

2. Reflexblase/ automat. Blase (aktiver spinaler Reflex)

Sy.: intermitt. Inkontinenz Kein Miktionsgefühl Kein Harndrang Keine willkürl. Miktion möglich Wenig Restharn Kleine, hypotone Blase	Urs.: Querschnittsy. BSP Myelitis intraspin. Tu Spin.Ischämie bei Aortendis-sektion

3. Dyssynerge Blase (Detrusor – Sphincter – Dyssynergie)

Sy.: Harninkontinenz u. Harnverhalt mäßig RH, Staccato- Miktion	Urs.: Hohe spinale Läsion unterhalb der Pons und oberhalb vegetat. Zentren

4. autonome Blase (Störung intramuraler Ganglien, Detrusorareflexie)

Sy.: Paradoxe Inkontinenz *(Ständiger Abgang kleiner Urinmengen)* Mictio durch Pressen Kein Harndrang Keine willkürl. Mictio Viel RH bei hypoton. Blase	Urs.: spinaler Querschnitt auf Höhe der vegetativen Zentren (Th 12- L2; S2 – S4)

Dr. Wolfgang Fische
Arzt für Neurologie/ Psychiatrie, Psychotherapie, Oberarztz, Univ.- Dozent Sozialmedizin an der Katholischen Universität Eichstätt

5. Überlaufblase (meist Afferenzstörung, gleiche Sy. auch bei Efferenzstörung)

Sy.: kein Harndrang Viel Restharn Blase aton, vergrößert	Urs.: Afferenzstörung: Diabet. Mellitus B-12 Mangel Syringomyelie Spinaler Schock Efferenzstörung: Poliomyelitis Polyradikulitis

6. Andere Ursachen d. Inkontinenz d. höheren Alters

- Beckenbodenanomalien (fkt. u. anat. z.B. nach Mehrfachgeburten)
- Prostatahypertrophie
- Rezidiv. Zystitiden

Harninkontinenz:

Diagnostische und therapeutische Standards notwendig.
Probleme der Geriatrie:

- Harninkontinenz im Alter ist so gut wie immer eineKombination aus altersbedingten Funktionseinbußen (-Änderungen) in Synergie mit
- nachlassender Mobilität, mit
- mnestisch-kognitiven Einbußen und mit
- Folgen der verschiedensten anderen Erkrankungen.

Zusätzlich:

Polymorbidität hat eine umfangreiche Pharmakotherapie zur Folge.

CAVE:

Inkontinenz als Nebenwirkung von Medikamenten!
(Therapie der Hypertonie, KHK, Gelenkbeschwerden, Schlafstörungen)

Wichtig:

Je höher der Grad der Multimorbidität des Patienten, desto höher die Wahrscheinlichkeit, Inkontinent zu werden.
Prävention und effiziente Therapie erfordern eine komplexe Einbeziehung möglichst vieler pathogenetischer Faktoren in die diagnostisch-therapeutische Strategie.
Hinsichtlich einer effizienten Präventionsstrategie richten sich die Bemühungen auf bekannte Risikofaktoren, bzw. Risikogruppen:

1. Aktivität im Alter beugt sogenannten „Alters- und Zivilisationskrankheiten" vor.
2. Bei Medikamenteneinsatz immer an die Nebenwirkung Inkontinenz denken!
3. Frauen mit Mehrfachgeburten entsprechend zu Beckenbodengymnastik, Blasen- und Miktionskontrolltraining anhalten.

Säulen des therapeutischen Vorgehens

nach gesicherter Diagnose!

Recura- Kliniken, Beelitz- Heilstätten, Deutschland

Zusammenführen von:
1. Verhaltensmedizinischen Erfahrungen
2. Physikalischen Maßnahmen
3. Medikamentösen Einflußmöglichkeiten
4. Operativen Techniken

Was ist für die Zukunft notwendig?
Entwicklung von Leitlinien zur Früherfassung und Behandlung der Inkontinenz
Daraus folgt:
* diese müssen einerseits den einfachen Mitteln der hausärztlichen Praxis genügen und andererseits
* eine hohe diagnostische Treffsicherheit aufweisen.

Hier sind sicher noch entsprechende Forschungsprojekte notwendig.

Zusammenfassung:

1. Harninkontinenz ist immer ein interdisziplinäres Problem
2. Harninkontinenz ist in der täglichen Praxis besonders ein Problem der älteren Patienten.
3. Grad der Multimorbidität korreliert mit der Wahrscheinlichkeit, inkontinent zu werden.
4. Harninkontinenz bedeutet, körperliche Beeinträchtigung, psychosoziale Beeinträchtigung und erhebliche finanzielle Aufwendungen für Diagnostik, Therapie und Pflege.
5. Notwendige Einführung entsprechender diagnostischer und therapeutischer Standards besonders zur Früherfassung, führt zu Kostenersparnisse sowohl im Bereich kassenärztlichen Praxis als auch in der stationären Versorgung und in der Pflege

The performance and assessment of hospital trauma teams

Andrew Georgiou[1] and David J Lockey[2]

Abstract

The purpose of the trauma team is to provide advanced simultaneous care from relevant specialists to the seriously injured trauma patient. When functioning well, the outcome of the trauma team performance should be greater than the sum of its parts. Trauma teams have been shown to reduce the time taken for resuscitation, as well as time to CT scan, to emergency department discharge and to the operating room. These benefits are demonstrated by improved survival rates, particularly for the most severely injured patients, both within and outside of dedicated trauma centres. In order to ensure the best possible performance of the team, the leadership skills of the trauma team leader are essential and their non-technical skills have been shown to be particularly important. Team performance can be enhanced through a process of audit and assessment of the workings of the team and the evidence currently available suggests that this is best facilitated through the process of video review of the trauma resuscitation. The use of human patient simulators to train and assess trauma teams is becoming more commonplace and this technique offers a safe environment for the future education of trauma team staff.

Trauma teams are a key component of most programmes which set out to improve trauma care. This article reviews the background of trauma teams, the evidence for benefit and potential techniques of performance assessment. The review was written after a PubMed, Ovid, Athens, Cochrane and guideline literature review of English language articles on trauma teams and their performance and hand searching of references from the relevant searched articles.

Introduction

Trauma is the leading cause of death in the 1-44 year old age group [1] and the fourth leading cause of death in the western world [2]. Despite the widespread recognition of simple principles of trauma care which have the potential to reduce mortality and the implementation of trauma education initiatives such as the American College of Surgeons Advanced Trauma Life Support courses (ATLS®) [3], the uptake and implementation of many of these principles has been sporadic and variable. In the UK for example, The Royal College of Surgeons of England highlighted important deficiencies in the management of severely injured patients in a report in 1988 [4]. A second report in 2000 [5] addressed the lack of ongoing improvement in the last six years of the twentieth century [6], recommending amongst other things, the introduction of a system of trauma audit and the establishment of hospital trauma teams. In 2007 a report by the UK National Confidential Enquiry into Patient Outcomes and Death [2] found that trauma teams were only available in 20% of hospitals, and a trauma team response was documented for only 59.7% of patients with injury severity scores (ISS) >16. The report strongly recommended that hospitals in the UK ensure that a trauma team is available twenty four hours a day, seven days a week. This problem is not confined to the UK. Data from Australia in 2003 show that only 56% of adult trauma hospitals [7] and 75% of tertiary

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Composition of the Trauma Team

The Core Trauma Team:
- Team Leader
- Anaesthetist
- Anaesthetic Assistant
- General Surgeon
- Orthopaedic Surgeon
- Emergency Room Physician
- Two Nurses. (Three if no anaesthetic assistant)
- Radiographer
- Scribe (Nurse or doctor)

Additional Essential Staff:
- Haematologist and Biochemist
- Blood Bank
- Porters

Additional Optional Staff (need identified during primary survey):
- Neurosurgeon
- Thoracic Surgeon
- Plastic Surgeon
- Radiologist

Figure 1. The typical composition of a trauma team. (Adapted from http://www.trauma.org webcite[12]).

paediatric hospitals which receive trauma [8] provided a trauma team reception.

The trauma team usually comprises a multidisciplinary group of individuals drawn from the specialties of anaesthesia, emergency medicine, surgery, nursing and support staff, each of whom provide simultaneous inputs into the assessment and management of the trauma patient, their actions being coordinated by a team leader. The primary aims of the team are to rapidly resuscitate and stabilise the patient, prioritise and determine the nature and extent of the injuries and prepare the patient for transport to the site of definitive care, be that within or outside the receiving hospital. This 'horizontal' approach to trauma care aims to provide rapid input to a critically injured patient without the need to contact and request the presence of individual team members. This aims to reduce the time from injury to critical interventions and surgery. The original aim of the trauma team was to reduce the second peak of the trimodal distribution of death following trauma, by appropriately managing correctable disturbances to the airway, breathing and circulation, which, if well implemented, was predicted to reduce preventable deaths by 42% [9]. The validity of the trimodal concept has since been questioned [10,11] but the likely benefits of coordination and rapid assessment of the trauma victims by a trauma team are widely accepted.

The Structure of the Trauma Team

A typical trauma team composition is shown in Figure 1[12]. It is important not to over-staff the trauma team; excessive numbers of people in the core team can lead to fragmentation, with individuals failing to adhere to the directions of the team leader. Additional team members do not necessarily improve team function [13]. There are wide regional and national variations in the composition of hospital trauma teams and there has been much work in assessing the optimal makeup and performance dynamics of the trauma team. The presence of a surgeon on the trauma team is considered by some to be essential. The availability of an attending trauma surgeon on the trauma team twenty four hours a day has been demonstrated to reduce resuscitation time and time to incision for emergency operations, but has not been demonstrated to impact on mortality [14]. Many centres now have a tiered trauma team response according to the severity of injury of the trauma patient. The application of triggering systems attempts to ensure that the appropriate tier of trauma team response is activated. The triggering system usually depends on the reported mechanism of trauma, the assessed injuries or the derangement in physiology noted on examination [15-17]. Information from pre-hospital care providers is useful for guiding the appropriate tier of response and for assembly and preparation of the trauma team [18]. Although these triggering systems serve as useful guide as to when the team should be activated, a considerable rate of over-triage, in the region of 30 to 50%, is deemed essential to prevent any under-triage and therefore delays in mobilising the team where it is deemed essential [19].

The leader of the trauma team must be experienced in the diagnosis and management of trauma patients and the likely pitfalls associated with dealing with severely injured patients. This individual must also be comfortable directing and being responsive to other team members. Non technical skills such as leadership are particularly important [20]; a good team leader will change his leadership style according to the experience of the team and the severity of the trauma [21]. Commonly the leader is an emergency physician, a surgeon or an intensivist-anaesthetist. Data comparing surgeons with other trauma team leaders such as emergency physicians, show no difference in the length of stay in the emergency department or in the actual or predicted survival of patients [22,23]. The seniority of the physician present has been linked to team performance [24] and is a key feature of trauma system development [2].

The Benefits and Pitfalls of a Trauma Team

Trauma systems have been shown to reduce mortality amongst the victims of trauma [25-29]. The trauma system is a multifaceted approach to trauma care involving professionals of many disciplines acting both pre-and in-hospital, within an organised model of care. The trauma team represents only one facet of the trauma system and separating the relative merits or drawbacks of the trauma team in isolation of the trauma system is not straightforward.

Data from Canada identifies that the involvement of the trauma team for patients with injury severity scores (ISS) >12 results in significantly better outcomes than if patients are dealt with on a service-by-service basis [30]. Not only was performance better than predicted, but there were more unexpected survivors in the group managed by the trauma team. Patients managed by a trauma team had higher ISS scores, were older, with more motor vehicle collisions and received more secondary transfers from other (non-trauma centre) hospitals, all of which should adversely affect the outcomes from this group, making the impact of the trauma team perhaps even more noteworthy. The incorporation of several specialties into one team therefore appears to be more valuable in outcome terms than the sum of its parts. The introduction of a trauma team in a level I trauma centre has been shown to reduce overall trauma mortality rates from 6.0% to 4.1% (absolute risk reduction 1.9%; 95% confidence interval 0.7%-3.0%), and in those severely injured patients with ISS scores >25, from 30.2 to 22.0% (absolute risk reduction 8.3%; 95% confidence interval 2.1%-14.4%)

[31]. Data shows that the trauma team also improves survival in hospitals not recognised as trauma centres [32].
Trauma teams also reduce times from emergency department arrival to CT scan, to the operating room and to emergency department discharge, manifesting as improved survival amongst critically injured paediatric patients. The mortality benefit is however lost in paediatric patients who have less severe injuries [33]. Conversely, those patients who meet well established trauma call criteria, but who are not treated by the trauma team (i.e. the team was not called) have a higher mortality; 28% of all trauma patients fell into this category in a study of 2539 consecutive patients from China [34]. Part of the benefit of the trauma team may be related to a reduction in time to definitive care (often haemorrhage control). When well organised, the trauma team has been shown to reduce total resuscitation time from 122 to 56 minutes [35]. The introduction of a trauma team and a trauma service led to a ten fold reduction (4.3% to 0.46%) in delayed injury diagnosis in the setting of paediatric trauma in Salt Lake City [36], but the exact contribution of the trauma team to this improvement is not clear.
Despite the huge associated socioeconomic burden of increased morbidity no data on the impact of the trauma team on morbidity exist. It is clearly very difficult to separate the impact of a trauma team on morbidity and isolate it from the care received from scene to hospital discharge - a lengthy and variable pathway for many severely injured patients.
The initial phase of hospital care in the emergency room has been identified as the area where most preventable problems in trauma care occur [37]. The trauma team is naturally implicated in many of these errors. Common problems include errors or delays in treatment, diagnosis, and intervention. Inadequate system capacity and poor processes are also frequently implicated. Data from Australia identify that 6.09 errors per fatal case occur in the emergency department with an alarming 3.47 errors directly contributing to patient death [38].
In paediatric trauma resuscitation, 5.9 errors per case have been shown to occur but with no fatalities directly attributable to the resuscitation phase [39]. Emergency room problems, errors or inadequacies are however less likely to occur in a trauma centre where 1.7 errors occurred per case as opposed to 5.1 per case in small regional hospitals ($p < 0.05$) [37].
Interestingly, errors seem more common before 8 pm when staffing levels and expertise are usually greatest [40]. Such errors are likely due to failure to perform therapeutic or diagnostic measures at the right time, with the correct frequency or in the right order [38]. Unfamiliarity with the trauma scenario, disorganization of staff or equipment, failure to prioritise or realise the complexity of the problem, fixation error or misdiagnosis [38] all contribute to what is a critical time in the passage of the patient through the trauma system. Errors in communication are estimated to occur in more than 50% of trauma resuscitations [41], and this together with inadequate documentation, were the main reasons for trauma team leaders underperforming [42].

Assessment of Trauma Team Performance

Evidence from the Scottish Trauma Audit Group has showed that the implementation of a trauma service audit programme can significantly improve survival in trauma patients. Survival rates for seriously injured trauma patients increased from 65 to79% through the course of the audit process, during which 53,000 trauma patients were seen in emergency departments in Scotland [43]. Assessment of the impact and performance of the trauma team as an isolated component of the trauma pathway is complex. Separation of the impact of multiple members of staff in a rapidly evolving environment with multiple variables is challenging and the optimal outcome measure that should be employed is open to debate.
Recording of error rates is somewhat crude and correlation of rates to outcome is fraught with confounding factors including assessor subjectivity and casemix variation. Assessment of single interventions rarely addresses the performance of a coordinated resuscitation attempt by professionals from different backgrounds. Carefully selected key performance indicators (e.g. time to CT scan) can be used to improve performance and set standards. Alternative outcomes may include compliance to local or published protocols [3], missed injury rates, improved outcomes and preventable deaths, all of which have benefits and drawbacks.
The optimal method of data acquisition during trauma team assessment has yet to be established. The options commonly employed are video review, observer review, medical notes review or the use of simulation. The remainder of this review will discuss the role for each.

Video

Video review of trauma team resuscitation has been shown to identify more errors than review of the medical notes. The retrospective review of medical notes has been shown to miss 80% of resuscitation errors identified through video review [39]. Video has been shown to be a more efficient use of review time which allows correction of conceptual as well as technical errors. Errors identified by video analysis are most commonly those relating to the airway, breathing, provision of oxygen and omissions in the secondary survey [39]. In the analysis of tracheal intubation in trauma, video review was able to identify performance errors such as failure of team coordination; poor communication, and omission of key tasks by team members. Poor recovery from errors has also been identified [44]. These findings have led to revised practices to improve the safety of tracheal intubation in trauma [44].
Careful scrutiny of the video data may yield further details of the resuscitation attempt which may prove difficult to obtain by other means. For example, team leader performance [45], time to procedural intervention [40,46], compliance with ATLS guidelines [47] and assessment of the use of universal precautions [40] have all been examined by video review in the past. Video has also allowed assessment of process errors and reasoning which were found to occur in every case, although they were only infrequently judged to result in adverse outcomes. However errors of omission were judged to be more severe [41]; these include failure to consider, observe or document, available relevant information in order to select appropriate care. This was found to occur at a frequency of 2.4 errors per case [48]. Video review has identified that poor team organisation results in a significant increase in error, whereas adequate pre-hospital report, evident and efficient leadership, continued supervision of

the patient, resuscitation in the correct order and working to defined protocols were each related to a lower total number of errors [40].

Review of videotaped trauma scenarios allows an appropriate source of feedback, debrief and learning for those concerned. In one study video review reduced the time to definitive care over a 3 month period by 13 minutes [49]. It has also allowed a retrospective review of the assessment of priorities during the resuscitation, the cognitive and physical integration of the workup by the team leader, team member adherence to assigned responsibilities, resuscitation time, errors or breaks in technique and behaviour change over time [49]. Through this process of performance review and retrospective learning, resuscitations have been shown to become more efficient and adherence to assigned responsibilities have improved [49]. Video data collection can be used to provide a quality appraisal system, for example during out-of-hours care, where no supervisor is available on site. The process of video review of trauma resuscitations therefore has benefits of performance and error analysis, audit and education, which together may manifest as an increase in patient survival [50].

There are potential disadvantages to the use of video in the assessment of trauma. Assessment of the vital signs from the video recording may be difficult and an appreciation of these signs is of course important for assessing the validity and timeliness of decisions made by the trauma team. This may be overcome by a direct vital sign stream to the video or by review of the medical records. The audio quality may be poor and analysis of events outside the field of view may be difficult [44]. Errors which are better identified through medical record review include errors such as drug or fluid dosing errors (particularly important in paediatric trauma) or changes to vital signs that fail to trigger an appropriate response from the team [39].

Confidentiality issues can exist in taking and storing data about patients from whom consent is often difficult to obtain. The use of retrospective consent may be difficult, given that the patient may be sedated for some time, or moved to alternative wards no longer under the remit of the emergency department where the video was recorded. However, multiple prestigious centres across the world have employed video review as a useful, educational, quality assurance tool with the approval of legal representatives, and so long as the data is erased in a timely fashion, this should pose few problems from a legal standpoint. The assessment of video data is usually performed by an expert panel with the assistance of published guidelines; this system is time consuming and may involve subjective bias.

Furthermore, delays in analysis may lessen the potential benefits of immediate feedback. It is also costly to establish and maintain and requires routine staff participation [51].

Simulator

Trauma team performance may be assessed using a simulator. Mannequins and simulators are increasingly being used in the assessment and education of critical care residents [52,53] and a similar approach may be appropriate in the assessment of trauma team performance.

Simulators have been used to facilitate educational goals such as communication, cooperation and leadership [54], which have already been identified as crucial qualities in trauma resuscitation [21]. A study of the use of an advanced human patient simulator (HPS) showed it to be a useful and reproducible tool for assessment of the trauma team [55], with the necessary use of video within the simulator to review team performance. Similarly, HPS has been used to demonstrate improvement in team performance following educational interventions such as an ATLS provider course or a rotation to a trauma centre. Significant improvements in critical treatment decisions, a reduced potential for adverse outcomes and improved team behaviour, function and efficiency have been observed following such interventions [55,56]. Simulators have also been used to facilitate educational on-site intervention of simulated paediatric trauma, to good effect [57]. HPS has been used to trial team behaviour assessment tools for application in trauma scenarios [58] which are thought to be important in team dynamics.

A learning curve exists in the use of simulation; the ability to interact with the simulator, 'role play' and verbalise requests for information requires some experience and this explanation may in part explain some of the improvements in team performance over time when simulation is used as the measurement tool. However, it allows exposure of the team to scenarios infrequently encountered in real life and provides a controlled, safe environment to learn from errors.

Observation by Third Party

Observation by a third party may yield selective or biased data [59]. It is useful if just one variable or individual is being examined, for example in assessment of the performance of the team leader [42], but one or two individuals cannot be expected to review overall performance where a horizontal rather than vertical model of care is applied. The observer requires a knowledge and understanding of the processes of trauma care and needs to be available at the time of trauma calls. Although this is a resource intensive approach a 'shadow' trauma team leader is a common training technique.

Medical Notes Review

Review of the medical notes is a slow and laborious process. Key information is often excluded from the notes [60] leading to a false negative error rate when assessing the performance of the trauma team. Essential elements of care such as the timeline, processes, communication, leadership, organisation, omissions and errors are difficult if not impossible to discern from medical record review. The contribution of professionals who do not usually enter information into the notes cannot be assessed and alternative considered diagnoses may not be recorded. For this reason the review of medical notes identifies only 20% of the errors seen on video review [39]. Furthermore, the ability to debrief, teach and learn is limited were the medical records alone are used.

Conclusions

The rapid development of trauma services has not been universal despite the high mortality rates in the young and the repeated reporting of suboptimal outcomes. Mortality reduction requires a comprehensive performance improvement programme [61] and an effectively performing trauma team is one contributing feature of good system

performance. As a component of the trauma service, the trauma team has been independently shown to reduce time in the resuscitation room, time to key investigations and to definitive care and reduce the rate of missed injury, all of which contribute to mortality reduction. If well audited, further reductions in mortality should be anticipated by education and by the introduction of processes to improve the workings of the team. Based on the limited evidence available the most effective method of trauma team audit and education appears to be by video review which can only be performed with careful consideration of consent and medicolegal issues. The use of human patient simulators may also provide a useful tool for the education of trauma team members.

Conflicts of interests

The authors declare that they have no competing interests.

Authors' contributions

AG and DL conceived the article concept. AG conducted the literature search and wrote the paper. DL reviewed, edited the paper and syntax.
Both authors have read and approved the final manuscript.

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Microelement homeostasis of the lymphatic region of organs by the pathology and phytocorrection on the sr rfa data

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Introduction

An interest to the problem of digestive and urinary excretion systems is caused wide broad of these pathologies among of adults. The pathology influences on many systems of organism. The lymphatic system of the organ plays leading role in homeostasis. At the present time the large anatomical and physiological materials about dependence of the lymph circulation and the state of the organ are accumulated. It may not be out of place to mark that the interconnection "organ - lymphatic node" is studied incompletely. The lymphatic node has the important place in providing homeostatic functions of drainage of the tissue microarea of the lymphatic region [1]. One of the important regulators is the full bodied composition of microelements. Last time the increased interest to the microelements activates studying this field. The microelements-antioxidants used for protection of the appearance and development of many diseases have the biggest popularity [2, 3, 4]. But to the last time the systematic studies of the role of microelements at the level of the structures of the lymphatic region are absent. Without understanding the regulated role of microelements into interconnection with the lymphatic system of organ it cannot be understand the mechanisms of the development of the pathology and to give proof the correction. These facts are the base of present study.

Materials and methods

The first experiment has made on the 310 white rats Wistar breed. The forming of the stomach ulcer has made with onetime intraabdominal injection of 2-3 mg/kg adrenaline [5]. The forming of the acute renal failure has made with onetime intramuscular injection of 50% glycerol's solution. The existence of the known models of the diseases has determined the duration of experiment. Herbal preparation formed as the mean of "background" therapy of the dysfunctions of organs. In experiment biologically active herbal preparation has used in the half of animals during two weeks before the injection. The phytocomposition is a know-how subject. The onetime dose is 0,1-0,2 g/kg. It has been used about 20 rats Wistar breed on every step of the study and in the control group.

Roentgen fluorescent analysis with synchrotron radiation (SR RFA) for the estimation of microelements in the biological objects (stomach, lymphatic node, blood) has made at the station of microelement analysis VEPP-3 of the Budker Institute of Nuclear Physics of Russian Academy of Sciences. Energy of monochromatic beam is 17 keV. The quantitative estimation of the emission spectrum of the objects of the study has made with "outer standard". Obtained data is analyzed with statistical method as regard to the control level.

Theoretical preconditions.

With developing clinic and prophylactic lymphology the great importance attaches to the lymphatic system with drainage-detoxication function. At that the lymphatic node is considered as a indicator of environment pressing [1]. On the base of it the methodology of the given study is defined the existing original concepts and scientific trends in rehabilitation medicine and in particularly in lymphology. First of all it is the concept of lymphatic region which units the tissue micro area of organ, nonvascular (tissue) and vascular ways, lymph nodes [1]; lympho(phyto) nutriciology which develops new phytomeans with lymphotropic qualities filling gap in feed structure with indispensable nutrients, microelements, vitamins and other biologically active substances, and also playing the role of some subsidiary "background" means of correction of the endoecological medium of organism [6]; biological element medicine which studies the role of the microelements in organism [7]. Exactly these conceptions are the base for studying the structures of the lymphatic region in the course of the stomach ulcer and for developing the lymphotropic correction with consideration of the microelement status.

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Results

The disturbance of the biological constants of the organism is connected with the remove from health to disease [8], which is very well demonstrated on the sample of the stomach and the kidney with the lymphatic system in the course of the pathology (ulcer of stomach, acute renal failure) and its correction with biologically active phytocomposition. Microelements because of their polyfunctional qualities play the main role among the many constants. The significant ones are microelements-antioxidants (selenium, copper, zinc et al.) which are used for antioxidant prevention at the conditions of physiologic and pathologic process. The content of the microelements changes depending on the duration of pathology and the correcting measures. It is shown an ambiguity of the distribution of microelements in the structures of lymphatic region at the different stages of the pathologic process. Proceed from the value of the content of microelements it is shown vector direction their accumulation (excessiveness or deficit) depending on the stage of study and studied structure in lymphatic region of

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organs for every studied microelement.

Ulcer of stomach.

In course of the ulcer process the copper content is insignificantly decreases on 5,6%-5,9% during the first 5 days. The copper transposition from tissue into intersticium (intercellular space) takes place in the course of the ulcer genesis. From the intersticium transport and resorption of the copper comes into blood stream. The first 5 days of study the increase of the copper content in the lymphatic system isn't shown and this content may be even negative (-4,2%) that is typical for 5th day of study. In course of the ulcer process the zinc content changes insignificantly in the stomach tissue, it is 3,4%-3,6% during the first 5 days. The zinc transposition from blood into intersticium is observed. The zinc value is increased on 22%-65,1%. It is observed the decrease of the zinc content on 17,18%-30,85% in the stomach tissue at the different stages of the ulcer process. The maintenance of the selenium level in the blood is dependent its deficit in the stomach tissue. The positive balance of the selenium content in the lymphatic node is observed, it is stable increased on 25,2%-54,5%.

The analysis of the content of microelements-antioxidants leads to the conclusion about different degree of the participation of them during the period of genesis and regeneration of the ulcer process in the stomach. Zinc and copper predominate quantitatively during the period of the active ulcer genesis and initial ulcer reparation that is the base for protection of the stomach cells from the oxidant stress. It is important because zinc in the big degree helps tissue heal and regeneration. It is revealed enough low selenium status in the stomach tissue. Functional selenium deficit accompanies the pathology of gastrointestinal tract [7]. A presence of the ulcer defect in the stomach is the inductor factor for so effector organ as a regional lymphatic node. The increase of all studied microelements particularly selenium and zinc take place in the lymphatic node.

Without understanding microelement homeostasis in interconnection with lymphatic system it is cannot understand the necessity of the use of lymphotropic phytopreparation for correction of the stomach ulcer process. The taking of phytopreparation changes the copper content in the structures of the lymphatic region of the stomach in according with the stages of study. At that condition negative value of the copper content is increased from -12,5% to -21,29% in the stomach tissue during the first 5 days of the stomach ulcer genesis. The taking of the phytopreparation maintains the level or enforces the changes of the zinc content in the structures of the lymphatic region in course of the ulcer process. The zinc content in the stomach tissue is increased in 2,1-3,7 times in comparison with its value in course of the ulcer process without correction with phytopreparation. At that time the taking of phytopreparation increases progressively the zinc content in the lymphatic node from 17,94% to 86,85%. The taking of phytopreparation during the first 5 days doesn't change the selenium deficit content in the stomach tissue, the content is on 28,5%-41% less than norm. The negative value of the selenium content in the blood shows on its transition into intersticium. The taking of phytopreparation enforces lymphatic drainage and leads to progressive increase of the selenium content in the lymphatic node from 16,2% to 129,5% at the end of study.

The using of lymphotropic phytopreparation for correction of the pathologic process accelerates the process of restitution [6]. The total character of microelement distribution in the structures of "lymphatic region" of stomach is maintained during the taking of phytopreparation. At that the content of studied microelement is progressively reached in the lymphatic system. It is connected with an enforced work of the lymphatic drainage mechanisms in course of the taking lymphotropic phytopreparation.

Acute renal failure.

Concentration of macro- and microelements changed in a tissue of a kidney and a regional lymph node at acute renal failure. There is in a kidney an increase in the content of, iron (in 1,4 times), copper (in 1,4 times), zinc and selenium (in 1,2 times) in an initial stage of development of acute renal failure (3 days). In an initial stage of development of acute renal failure (3 days) in a regional lymph node there is an increase in the maintenance of iron (in 1,5 times), zinc (in 1,3 times). Decrease of the content of copper (in 1,5 times) and selenium (in 1,6 times) in a lymph node is simultaneously observed in comparison with control. At a pathology a kidney accumulate microelements in a greater degree, than lymph nodes. Accumulation of microelements in kidney and lymph node tissue assumes their deposition for loss prevention with urine at a pathology of kidneys. Application of herbal medicine changes a microelement profile of a kidney and a regional lymph node at acute renal failure.

In an initial stage of development of acute renal failure (3 days) herbal medicine leads to increase in the content of iron (in 1,7 times), selenium (in 1,2 times) in a kidney. Decrease 1,1 times of concentration of zinc, other element is simultaneously observed (copper) have not changed the content in comparison with control. In an initial stage of phytocorrection of acute renal failure (3 days) in a lymph node there is a decrease of the content of selenium (in 2,9 times) is observed, other elements (iron, copper, zinc) have not changed the content in comparison with control.

The raised content of microelements testifies to their necessity for content of a structurally-metabolic homeostasis at development of acute renal failure. Pays attention to increase of microelements-antioxidants during the sharp period of acute renal failure. They are necessary to realization of nephroprotection. The increase in the content of separate microelements can serve as an indirect indicator of functional activity of cells. It is activated by microelements about third of known enzymes [7].

Conclusion

Lymphatic system and microelement status play the specific role in the maintenance of homeostasis at the pathology [1, 7]. Microelement balance in the structures of lymphatic region of organs depends on the stage (period) of the pathological process and reflects the microelement circulation in system "blood – intersticium (organ) – lymphatic node". It takes place the specific distribution of microelements connecting with their various contributions in metabolic status of studied biologic objects. The taking of lymphotropic phytopreparation leads to the

quick restitution of organ [6] on the background of final stabilization of microelement content in the organ tissue and their progressive increase in the lymphatic system. Forming microelement status is directly connected with drainage detoxication and immune functions of the lymphatic node which are enforced during the taking of phytopreparation. The using of phytopreparation as a diet modifying mean of "background" correction of the pathology and according dysmicroelementosis is obvious.

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Ergebnisse einer Umfrage zu angewandten Qualitätsstandards in nicht-interventionellen Studien unter den Mitgliedsunternehmen des Verbandes der forschenden Pharma-Unternehmen in Deutschland

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Einführung

In der Diskussion über die Wirksamkeit und Sicherheit von innovativen Arzneimitteln kommt der Gewinnung von zusätzlichem wissenschaftlichem Erkenntnismaterial nach der behördlichen Zulassung eines Medikamentes eine immer größere Bedeutung bei der umfassenden Beurteilung einer neuen therapeutischen Option zu.

Die Wirksamkeit, neben Verträglichkeit und Sicherheit, eines Arzneimittels belegen die Ergebnisse aus kontrollierten klinischen Prüfungen der Phasen II und III an einer begrenzten Anzahl an Patienten unter definierten Behandlungsbedingungen und unter Berücksichtigung strikter gesetzlicher Anforderungen sowie der Grundsätze der „Guideline for Good Clinical Practice" der International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [1]. Die behördliche Zulassung eines Medikamentes beruht auf einer positiven Beurteilung des Nutzen-/Risikoverhältnisses des Arzneimittels für eine bestimmte Zielpopulation in einer spezifischen Indikation.

Die Richtlinie 2001/20/EG in Artikel 2 (c) [2] und das deutsche Arzneimittelgesetz (AMG) in § 4 Abs. 23 [3] definieren in Abgrenzung zur klinischen Prüfung die nicht-interventionelle Prüfung. Synonym hierzu wird in § 67 Abs. 6 AMG der Begriff Anwendungsbeobachtung (AWB) eingeführt. Nach Erlangung der Zulassung können nicht-interventionelle Studien (NIS)/AWB dem zusätzlichen Erkenntnissgewinn bei der routinemäßigen Anwendung von Arzneimitteln im klinischen Alltag dienen.

Bereits während des klinischen Studienprogramms ist das Erkennen möglicher Signale seltener unerwünschter Ereignisse in der Zielpopulation selbst oder das Identifizieren möglicher Risiken in Subgruppen der Zielpopulation eine zentrale Aufgabe der Arneimittelsicherheit eines pharmazeutischen Unternehmens. Gibt es hinreichende Hinweise für derartige Signale oder Risiken, sieht die europäische Legislative ein weiterführendes sorgfältiges Nachverfolgen der beobachteten Anzeichen im Rahmen eines Risk Management Plans (RMP) [4] vor. Ein wesentlicher Bestandteil des RMP ist die Beobachtung und Bewertung der erkannten Signale und Risiken nach der Zulassung unter Alltagsbedingungen in einer wesentlich größeren Patientenpopulation als in dem vorangegangenen klinischen Studienprogramm. Hierbei kommen Post-Authorisation Safety Studies (PASS) eine besondere Bedeutung zu. PASS wurden zuerst definiert in der Richtlinie 2001/83/EC [5] und sind seit 2008 im europäischen Recht durch das Volume 9A [4] als ein möglicher Bestandteil des Risk Management Plans vorgesehen. PASS können entweder als klinische Prüfungen der Phase IV oder als NIS/AWB konzipiert sein.

Voraussetzung für die Durchführung als NIS/AWB ist, dass die üblichen Qualitätsanforderungen der Fachgesellschaften für epidemiologische Studien auf internationaler Ebene

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[6], [7] wie auch auf nationaler Ebene [8] beachtet werden, wohingegen die Grundsätze der GCP-Leitlinie bei NIS/AWB entsprechend Part I, Kapitel 7.1 des Volume 9A der Guidelines on Pharmacoviligance der Europäischen Kommission [4] keine Anwendung finden.
In Deutschland folgen NIS/AWB zudem den Regelungen und Vorgaben des § 67 (6) des Arzneimittelgesetzes [3] sowie den Empfehlungen der Bundesoberbehörden [9]. Zusammen mit den Empfehlungen des Verbandes der forschenden Pharma-Unternehmen (vfa) [10] und den Empfehlungen des Bundesverbandes der Pharmazeutischen Industrie (BPI) [11] sowie weiterer Empfehlungen [12] definieren diese einen Qualitätsstandard bzw. State of the Art bei NIS/AWB, welcher die Validität der erhobenen Daten und der Ergebnisse aus diesen Untersuchungen in die Nähe der von klinischen Prüfungen rückt.
In zwei Umfragen in den Jahren 2008 und 2010 wurde die Umsetzung der Inhalte der genannten Empfehlungen und gesetzlichen Regelungen in den Mitgliedsfirmen des vfa untersucht. Die Ergebnisse der aktuellen Umfrage werden in der vorliegenden Arbeit vorgestellt, diskutiert und mit den Ergebnissen aus dem Jahre 2008 verglichen.

Methodik

Um zu ermitteln welche Qualitätsstandards bzw. qualitätssichernden Maßnahmen in den forschenden pharmazeutischen Unternehmen bei der Planung, Durchführung und Auswertung von NIS/AWB angewandt werden, führte eine Arbeitsgruppe des vfa-Unterausschusses Klinische Forschung/Qualitätssicherung und der Clinical Quality Assurance Germany (CQAG) im Februar und März 2008 eine detaillierte Umfrage unter den Mitgliedsfirmen des vfa durch [13]. Die Fragen bezogen sich im Wesentlichen auf den Stand der Umsetzung und Einhaltung der vfa-Empfehlungen aus dem Jahre 2007.
Um die Nachhaltigkeit der vfa-Empfehlungen und der eingeleiteten qualitätsverbessernden Maßnahmen aus dem Jahre 2007 zu überprüfen sowie den aktuellen Standard in der Durchführung von NIS/AWB bei den Mitgliedsfirmen des vfa zu erheben, nutzte die Arbeitsgruppe einen vergleichbaren, ergänzten Fragebogen für eine erneute Umfrage im Mai und Juni 2010.
Die Fragen bezogen sich auf allgemeine Bereiche wie
• die Bewertung der Wichtigkeit von NIS/AWB durch das Unternehmen,
• die Art und Anzahl laufender Projekte, die Existenz entsprechender Verfahrensanweisungen oder Standard Operating Procedures (SOP) und
• die durchgeführten bzw. vorgesehenen Schulungsmaßnahmen für die beteiligten internen und externen Mitarbeiterkreise zu diesen Regelungen und Vorgaben.
Gefragt wurde weiterhin nach spezifischen Maßnahmen
• in der Planungsphase einer NIS/AWB, z.B. Überlegungen zur Repräsentativität der Studienzentren, und
• in der Auswertungsphase, z.B. bei der Dateneingabe, dem Datenmanagement und der statistischen Auswertung.
Zugleich wurden die Unternehmen nach ihren Erfahrungen mit dem Beratungsverfahren bei NIS, insbesondere AWB, durch die zuständige Ethik-Kommission, der durchschnittlichen Dauer des Verfahrens und dessen Ergebnisses befragt.
Ein umfangreicher Fragenkomplex widmete sich den vorgesehenen und den tatsächlich angewandten Maßnahmen während der Durchführungsphase, im Besonderen bezüglich
• der Selektion der Studienzentren,
• der Bilanzierung der Rücklaufquote und
• der vorgesehenen Maßnahmen für den Fall, dass die Rücklaufquote hinter den Erwartungen zurückbleiben würde.
Ebenfalls umfassend befragt wurden die teilnehmenden Unternehmen zu den Themen
• Einwilligungserklärung der Patienten in NIS/AWB,
• Verifizierung der erhobenen Daten,
• vorgesehene Qualitätskontroll- und Qualitätssicherungsmaßnahmen sowie
• Auditaktivitäten.
Transparenzmaßnahmen, insbesondere die Veröffentlichung von Informationen über geplante und laufende NIS-/AWB-Projekte und die Art und Weise der Veröffentlichung der Ergebnisse aus diesen Untersuchungen bildeten einen weiteren Fragenkomplex.
Die Möglichkeit zu Mehrfachnennungen in einigen Fragenkomplexen begründet die in den Tabellen 2 bis 6 über die Zahl von n=28 bzw. über 100% hinausgehenden Summen der Antworten.

Umfrage

Im April 2010 wurden die 46 Mitgliedsfirmen des vfa angeschrieben und um ihre Teilnahme an der Umfrage gebeten. Bis Anfang Juni 2010 lagen Rückmeldungen aus 36 Firmen vor, dies entspricht einer Quote von 78% der befragten Firmen. Hiervon gaben 8 Unternehmen an, vorwiegend biotechnologische Unternehmen, keine NIS/AWB durchzuführen, da sie bis zu diesem Zeitpunkt noch für keines ihrer Entwicklungsprodukte eine Marktzulassung erlangt hatten. Die detaillierte Auswertung der Ergebnisse dieser Umfrage bezieht sich auf die ausführlichen Rückmeldungen aus 28 Unternehmen, die tatsächlich solche Untersuchungen durchführten oder grundsätzlich hierzu die Möglichkeit gehabt hätten. Aufgrund der Größe dieser Unternehmen und des beschriebenen Umfangs ihrer Forschungsaktivitäten sind diese als repräsentativ für alle vfa Mitgliedsunternehmen bzw. gleichfalls als repräsentativ für diese Formen der epidemiologischen Forschung in Deutschland anzusehen.

Ergebnisse

Art und Anzahl nicht-interventioneller Studien
In allen Rückmeldungen (n=28) der befragten Unternehmen wurden NIS als „wichtige und notwendige Untersuchungsformen nach der Zulassung eines Arzneimittels“ bezeichnet. Für 4 Firmen traf dies allerdings nicht auf AWB selbst zu, sondern ausschließlich auf die Kategorie NIS. Ein Unternehmen gab hierzu erklärend an, dass dies durch die „mangelnde (öffentliche und behördliche) Akzeptanz“ von AWB begründet sei.
In einem Großteil der Unternehmen (n=21) sind AWB zugleich Bestandteil des Risk Management Plans eines Arzneimittels.
Die Zahl der von den befragten Mitgliedsunternehmen

durchgeführten Studien und die Untersuchungsformen sind in Tabelle 1 [1] zusammengefasst. Diese werden den Ergebnissen der Umfrage aus dem Jahre 2008 gegenübergestellt.

Die absoluten Zahlen in Tabelle 1 [1] sind als Momentaufnahmen zum Zeitpunkt der beiden Umfragen zu verstehen. Bei der Betrachtung der pro Unternehmen durchschnittlich durchgeführten NIS insgesamt lässt sich tendenziell ein Anstieg von =8,3 im Jahre 2008 auf =10,1 im Jahre 2010 feststellen, die Zahl durchschnittlich pro Unternehmen durchgeführter AWB hingegen sinkt im selben Zeitraum von =7,1 auf =5,8.

Standard Operating Procedures, Verfahrensanweisungen

Ein wesentlicher Bestandteil des Qualitätsmanagements ist das Vorhandensein umfassender, schriftlicher Verfahrensanweisungen und/oder Standard Operating Procedures (SOP). Diese nehmen idealerweise Bezug auf internationale wie auch auf nationale Regularien, Leitlinien und Empfehlungen zu NIS/AWB. Es gaben 22 Unternehmen (79%) an, NIS SOP auf internationaler Ebene zu besitzen, in 10 Unternehmen (36%) existierten NIS SOP auf internationaler wie auch auf nationaler Ebene. Spezifische, deutsche AWB SOP wurden in 21 Unternehmen (75%) erstellt; 6 Firmen (21%) sehen die Thematik und Verfahrensabläufe hinreichend in ihren internationalen SOP berücksichtigt. In 26 Unternehmen (93%) sah man den Bezug der SOP-Systeme zu den einschlägigen Empfehlungen und Regularien in Deutschland als gegeben an.

Ein Unternehmen beauftragte ausschließlich externe Dienstleister, Contract Research Organisations (CRO), mit der Durchführung von NIS/AWB, die hierfür eigene SOP erstellt und angewandt hatten.

Schulungsmaßnahmen

Zur Vermittlung der NIS SOP-Inhalte bedienen sich die befragten Unternehmen einer Fülle unterschiedlicher Methoden mit tatsächlichen bzw. vorgesehenen Wiederholungs- oder Auffrischungsintervallen. In allen Firmen (n=28) wurden die Mitarbeiter der medizinischen Bereiche über die SOP-Inhalte und die zugrunde liegenden Regularien geschult. Zwei Firmen gaben an, diese Schulung im halbjährlichen, 10 Firmen in jährlichem Rhythmus zu wiederholen. Alle anderen Unternehmen sahen eine Schulung vor jedem neu zu startenden Projekt vor. Die hauptsächlich angewandte Schulungsmethode war die Präsenzschulung (n=22). In 9 Fällen wurde die Schulung in Form von E-Learning-Modulen alleine oder in Verbindung mit einer Präsenzschulung gewählt. Neue, geänderte oder aktualisierte Regularien waren nach Angaben der Mehrheit der befragten Unternehmen ein Auslöser, eigene SOP oder Verfahrensanweisungen entsprechend zu aktualisieren und in Folge Schulungsmaßnahmen vorzusehen.

In 23 Unternehmen wurden keine NIS/AWB-spezifischen Schulungsmaßnahmen für die Bereiche Marketing sowie für den Kreis der Pharmaberater durchgeführt. Folgende Gründe wurden hierfür angegeben: einerseits würde die Funktion des Pharmaberaters in seiner bisherigen Form nicht mehr existieren, das heißt die Aufgaben würden durch einen spezialisierten, wissenschaftlichen Außendienst wahrgenommen. Andererseits wurde die Durchführung von NIS/AWB zunehmend an externe Dienstleister übertragen, eine intensive projektbezogene Schulung für Marketing und Pharmaberater erschien deshalb nicht mehr angemessen. Selbstverständlich würde in diesen Fällen eine vorherige Schulung der beim Dienstleister mit dem Projekt befassten Mitarbeiterkreise durchzuführen sein.

Verantwortlichkeit im Unternehmen

In allen befragten Unternehmen (n=28) war die organisatorische Gesamtverantwortung für die Erstellung des Studienplans, die Projektdurchführung, die zeitgerechte Auswertung und Veröffentlichung der Zusammenfassung der Studienergebnisse sowie die Budgetverantwortung bei NIS/AWB im Bereich Medizin unter der Verantwortung des Leiters dieses Bereiches verankert.

Selektion und Rekrutierung der Studienzentren und Verteilung der Studienunterlagen

In Abhängigkeit von der vorgesehenen Zahl von Studienzentren und der zu beobachtenden Patienten und in Abhängigkeit von der untersuchten Indikation ergaben sich für die Unternehmen unterschiedliche Überlegungen zur Selektion geeigneter Studienzentren. In Untersuchungen mit einer großen Anzahl teilnehmender Zentren in einer breit vorkommenden Indikation wurde angestrebt, eine möglichst gleichmäßige geographische Verteilung zu erreichen. Dies konnte in der Regel durch eine nicht restriktive Auswahl von Zentren ohne zugrunde gelegte Selektionskriterien erreicht werden.

Bei Untersuchungen in einer seltenen Indikation mit einer geringen Zahl spezialisierter Zentren dienten firmeneigene Kenntnisse über Erfahrungen der teilnehmenden Ärzte in der Indikation sowie Internetinformationsquellen oder kommerziell vertriebene Ärztedatenbanken mit Angaben der medizinischen und therapeutischen Ausrichtung der jeweiligen Einrichtung oder Praxis als Selektionsgrundlage geeigneter Zentren.

Die Platzierung der Unterlagen wurde in 20 Unternehmen über CRO vorgenommen, in 15 Unternehmen von Mitarbeitern des Bereichs Medizin. Neun Firmen machten von beiden Möglichkeiten Gebrauch. Sieben Unternehmen beauftragten über ihren Bereich Medizin ausschließlich CRO mit der Platzierung der Unterlagen (Tabelle 2 [2]).

Als Beispiele für effiziente Auswahlverfahren geeigneter Zentren wurden Fragebogen genannt, in denen vorab die grundsätzliche Teilnahmebereitschaft, die Behandlungshäufigkeit der zu beobachtenden Patientenpopulation sowie spezielle Ausstattungs- oder Praxischarakteristika erfragt wurden. Hierdurch ließ sich eine gezielte Einbeziehung von Zentren erreichen, die mit einer hohen Wahrscheinlichkeit zu einer qualitativ angemessenen Durchführung der vorgesehenen Untersuchung in der Lage waren.

Im Beobachtungsplan einer NIS/AWB wurde in allen Unternehmen das Ende der Untersuchung angegeben. Ebenfalls in allen Unternehmen wurden Maßnahmen für die Fälle vorgesehen, in denen die Rücklaufquote der Dokumentationsunterlagen zunächst unter der erwarteten Quote bleiben würde.

Transparenz in der Forschung

Um die Transparenz in der Forschung mit Arzneimitteln zu gewährleisten, werden Informationen zu kontrollierten klinischen Prüfungen vor der Zulassung sowie Angaben über

durchgeführte NIS/AWB nach Erteilung der Zulassung in öffentlich zugänglichen Registern publiziert. Die befragten Unternehmen nutzten hierfür verschiedene Foren, die in Tabelle 3 [3] dargestellt sind. Die Veröffentlichung der Zusammenfassung der Ergebnisse aus NIS/AWB erfolgte in den in der Tabelle 4 [4] genannten Internetregistern.

Ethik-Kommissionsverfahren

Die vfa-Empfehlungen und die Empfehlungen des BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte)/ PEI (Paul-Ehrlich-Insitut) sehen eine Beratung vor der Durchführung von prospektiv angelegten NIS/AWB durch eine unabhängige Ethik-Kommission vor. Dies entspricht der in einigen Ärztekammern, beispielsweise der bayerischen Landesärztekammer, berufsrechtlich verankerten Beratungspflicht [14] vor der Durchführung epidemiologischer Forschungsvorhaben. Die für ein Forschungsprojekt zuständige Ethik-Kommission ergibt sich aus der Benennung des ärztlichen Studienleiters, der die wissenschaftlich medizinische Leitung der Untersuchung übernimmt. In 21 Unternehmen (75%) wurde hierzu ein externer, nicht dem Unternehmen angehörender, ärztlicher Studienleiter benannt. Drei Firmen (11%) benannten ausschließlich interne ärztliche Studienleiter. In 4 Fällen (14%) wurden sowohl externe als auch interne Studienleiter benannt.

Auf die Frage nach Erfahrungen mit ablehnenden Beratungsergebnissen antworteten 19 Unternehmen (68%) mit „nein".

In 9 Fällen wurde diese Frage mit „ja" beantwortet. Als Gründe für ein ablehnendes Beratungsergebnis wurden vorwiegend konträre Einschätzungen bezüglich des nicht-interventionellen Charakters der eingereichten NIS/AWB zwischen dem einreichenden ärztlichen Studienleiter und der zuständigen Ethik-Kommission genannt.

Auf die Frage nach sonstigen Erfahrungen mit dem Ethik-Kommissionsverfahren und ggf. dem Dialog mit der zuständigen Ethik-Kommission wurden zudem folgende Aspekte genannt: In 5 Beispielen wurden die eingereichten Unterlagen durch die für den ärztlichen Studienleiter zuständigen Ethik-Kommissionen für nicht beratungspflichtig angesehen. Dies hatte zur Folge, dass der ärztliche Studienleiter gewechselt wurde, um den Empfehlungen der Bundesoberbehörden und des vfa Genüge zu tun.

Die Frage nach der Anerkennung eines bereits für den ärztlichen Studienleiter vorliegenden Beratungsergebnisses durch weitere, für teilnehmende Zentren zuständige Ethik-Kommissionen ließ sich bislang nicht eindeutig klären. Hierbei wurden sowohl Fälle genannt, in denen eine Anerkennung der Erstberatung erfolgte als auch Fälle mit der Notwendigkeit einer erneuten Beratung.

Des Weiteren gaben 3 Unternehmen an, dass zu den geforderten Antragsunterlagen für eine Ethik-Kommissionsberatung die Lebensläufe teilnehmender Ärzte aus dem Bereich der entsprechenden Landesärztekammer gehörten. Eine schlüssige Begründung für diese Forderung stand aus Sicht der Unternehmen aus.

Patienteneinwilligung und Verifizierung der Daten

Sowohl die vfa-Empfehlungen als auch die Empfehlungen der Bundesoberbehörden sehen eine schriftliche Einwilligung des Patienten in die Teilnahme an einer prospektiven NIS/AWB vor. Für eine Verifizierung der erhobenen Daten mittels Einsichtnahme in die Originaldokumentation, beispielsweise der Krankenakte des Patienten, durch Firmenangehörige oder Beauftragte, ist die ausdrückliche Zustimmung des Patienten zwingend erforderlich. Eine Datenverifizierung wäre jedoch auch in Form eines Telefoninterviews oder durch die Interviewtechnik zwischen Firmenangehörigem und teilnehmendem Arzt möglich ohne eine unmittelbare Einsichtnahme in die Patientendokumentation. In der Umfrage wurde dieser Themenkomplex ausführlich abgefragt, die Ergebnisse sind in den Tabelle 5 [5] und Tabelle 6 [6] dargestellt. Die Möglichkeit zu Mehrfachnennungen erklärt hierbei die über n=28 bzw. über 100% hinausgehenden Ergebnisse.

Unabhängige Qualitätssicherungsmaßnahmen

Auch in NIS, die definitionsgemäß [4], [12] nicht nach den GCP-Grundsätzen durchzuführen sind, können stichprobenartige, systematische Auditmaßnahmen durch firmeninterne, unabhängige Qualitätssicherungseinheiten der Überprüfung der ordnungsgemäßen und regelkonformen Studiendurchführung dienen. Befragt nach den bei NIS/AWB durchgeführten Auditmaßnahmen antworteten jeweils 20 Unternehmen (71%), dass sie sowohl firmeninterne Systemaudits wie auch Audits der von ihnen beauftragten CRO durchführten. Jeweils 6 Firmen sahen diese Art von Audits nicht vor, 2 Firmen machten hierzu keine Angaben.

In der Umfrage gaben 8 Unternehmen (29%) an, Auditaktivitäten auch vor Ort an teilnehmenden Studienzentren durchzuführen. Im Jahre 2008 wurden solche Auditmaßnahmen lediglich von 2 Unternehmen (11%) vorgesehen. Hier zeigte sich demzufolge ein ansteigender Trend. Hingewiesen wurde jedoch darauf, dass Auditmaßnahmen an Studienzentren nicht allgemein und in allen NIS/AWB gleichermaßen vorgesehen waren, sondern im Wesentlichen beschränkt waren auf solche NIS/AWB, die aufgrund behördlicher Anforderungen als PASS durchgeführt wurden.

Aufwandsentschädigung

Alle Empfehlungen sowie das AMG sehen vor, „Entschädigungen, die an Ärzte für ihre Beteiligung an Untersuchungen … geleistet werden, … so zu bemessen, dass kein Anreiz für eine bevorzugte Verschreibung oder Empfehlung bestimmter Arzneimittel entsteht" [3]. Als Grundlage zur Berechnung der Entschädigung wurde in der Regel die Gebührenordnung der Ärzte herangezogen. Die Höhe der Entschädigung richtete sich nach dem tatsächlich erbrachten Dokumentationsaufwand zusammen mit dem zeitlichen Aufklärungsbedarf über die datenschutzrechtlichen Aspekte hinsichtlich der Weitergabe und Verarbeitung der erhobenen Daten durch den Auftraggeber der NIS/AWB.

Keines der befragten Unternehmen sah eine pauschale Aufwandsentschädigung ohne Berücksichtigung der tatsächlich erbrachten Dokumentations- und Aufklärungsaufwandes vor. In jeweils 21 Fällen wurde eine Aufwandsentschädigung nach vollständig dokumentierten Visiten oder vollständigen Dokumentationsbogen angegeben. In 14 Fällen wurde von beiden Möglichkeiten

jeweils in Abhängigkeit von der Dauer der NIS/AWB und der Komplexität der Dokumentation Gebrauch gemacht.
Empfohlen wurde zudem, den zu erwartenden zeitlichen Aufwand in Form eines Tests mit den beteiligten Ärzten und dem nicht-ärztlichen Personal an potenziellen Studienzentren zu evaluieren. Berücksichtigung finden muss auch der hierfür erhöhte zeitliche Aufwand am Studienzentrum für die Fälle, in denen eine Qualitätskontrolle der erhobenen Daten durch den Auftraggeber vorgesehen ist.
Datenmanagement und Auswertung der Ergebnisse
Die Angaben zu durchgeführten Maßnahmen bei der Erfassung, Eingabe und Auswertung der erhobenen Daten aus NIS/AWB sind in Tabelle 7 [7] zusammengefasst.
In allen Unternehmen wurden regelmäßig qualitätssichernde Instrumente und Methoden wie ein vorab erstellter statistischer Analyseplan, eine routinemäßige Plausibilitätskontrolle sowie die Verwendung so genannter Queries bzw. Nachfragen bei unklaren oder fehlenden Daten angewandt.
Sieben Unternehmen gaben an, ausschließlich eine doppelte Datenerfassung bei der Eingabe der Daten vorzunehmen. In 9 Unternehmen wurden sowohl eine doppelte wie auch eine einfache Datenerfassung vorgesehen.

Diskussion

NIS/AWB werden von den forschenden Pharma-Unternehmen als leistungsfähige, epidemiologische Instrumente zur Erlangung eines zusätzlichen Erkenntnisgewinns über die Anwendung eines Arzneimittels nach dessen behördlicher Zulassung anerkannt und genutzt. Sie sind von den Bundesoberbehörden in Deutschland akzeptierte und in der Fachöffentlichkeit diskutierte Untersuchungsformen [15], [16], [17] zur Gewinnung zusätzlicher Erkenntnisse zur Sicherheit eines Arzneimittels nach dessen Markteinführung. In Abstimmung mit nationalen und internationalen Aufsichtsbehörden können NIS/AWB zudem durchgeführt werden, um Erkenntnisse zu potenziellen Sicherheitsrisiken aus dem klinischen Entwicklungsprogramm einer Substanz in weiterführenden Post-Authorisation Safety Studies [4] zu überprüfen.
Dem wissenschaftlichen Charakter dieser Untersuchungen Rechnung tragend, liegt die Gesamtverantwortung für NIS/AWB in den vfa-Mitgliedsunternehmen bei der Leitung der medizinischen Abteilung des jeweiligen Unternehmens. Dieser zentrale, organisatorische Aspekt, der bereits in der Vorumfrage aus dem Jahr 2008 erfasst wurde, konnte durch die Ergebnisse dieser aktuellen Umfrage aus dem Jahr 2010 bestätigt werden.
Die in der Umfrage genannten Maßnahmen zur Qualitätskontrolle und Qualitätssicherung, beispielsweise bei der Verifizierung der erhobenen Daten, der Dateneingabe und -erfassung sowie der biometrischen Auswertung rechtfertigen zudem ein hohes Maß an Vertrauen in die Validität der erhobenen Daten und der daraus gewonnen Ergebnisse.
Die Veröffentlichung von Informationen über die Durchführung von NIS/AWB auf öffentlich zugänglichen Internetportalen dient zudem der Sicherstellung der Transparenz in diesem Forschungssektor. Hierfür nutzen alle befragten Firmen bereits existierende Internetseiten oder haben eigene Informationsseiten entwickelt. Dasselbe gilt für die Veröffentlichung der Zusammenfassung der Ergebnisse gemäß internationaler Standards [18] innerhalb von 12 Monaten nach Abschluss der NIS/AWB. Eine Überprüfung durch die Autoren ergab im Juli 2010, dass in keinem Falle der im vfa-Internetregister veröffentlichten NIS/AWB eine Überschreitung dieser Frist festzustellen war.
Die vorherige Beratung von NIS/AWB durch die für den ärztlichen Studienleiter zuständige Ethik-Kommission zusammen mit der Aufklärung und Einwilligung des Patienten über die anonymisierte Datenerhebung und -weitergabe bilden weitere Grundlagen für medizinisch wissenschaftlich fundierte und ethische Untersuchungen.
Es zeigt sich, dass die Empfehlungen der Verbände vfa und BPI zusammen mit den Empfehlungen der Bundesoberbehörden und weiteren Ansätzen [12] einen wichtigen Beitrag leisten konnten, das Instrument der NIS/AWB als Teil der wissenschaftlichen epidemiologischen Forschung mit Arzneimitteln im Sinne von Guter Epidemiologischer Praxis weiter zu verbessern.
Des Weiteren konnte die aktuelle Umfrage bestätigen, dass die vfa-Mitgliedsunternehmen seit der Veröffentlichung der vfa-Empfehlungen im Mai 2007 diese Selbstverpflichtung in allen wesentlichen Aspekten erfolgreich umsetzen konnten. Die Ergebnisse der Umfrage aus dem Jahr 2008, die bereits wenige Monate nach der Veröffentlichung der vfa-Empfehlungen erfolgte, konnten damit bestätigt werden.
Die Empfehlungen der Verbände und Bundesoberbehörden bilden gleichfalls eine Basis für angewandte Qualitätsstandards bei NIS/AWB, die sich den Qualitätsvorgaben für klinische Prüfungen weiter angenähert haben. Aufgrund des unterschiedlichen Charakters dieser Forschungsformen sowie unterschiedlicher nationaler gesetzlicher Regelungen für klinische Prüfungen einerseits und NIS/AWB andererseits, sind der jeweiligen Forschungsform angemessene qualitätssichernde Maßnahmen anzuwenden. Es ist hierbei klar zu unterscheiden zwischen den gesetzlichen und regulatorischen Anforderungen an Studien gemäß der Grundsätze zu „Good Clinical Practice“ und Nicht-GCP-Studien.
Beispielsweise können auch in Nicht-GCP-Studien Audits durch unabhängige Qualitätssicherungseinheiten sachgerechte Maßnahmen darstellen, werden jedoch in ihrem Umfang und in ihrer Ausführung immer den Dimensionen und Anforderungen von NIS/AWB gerecht werden müssen. Eine Überprüfung der regelkonformen Durchführung von NIS/AWB durch externe Dienstleister darf regelmäßig vor und während des Verlaufs der Untersuchungen als sinnvoll und notwendig angesehen werden, um die Einhaltung der unternehmenseigenen Standards auch durch Dritte sicherstellen zu können. Jedoch bedürfen Audits an teilnehmenden Studienzentren einer kritischen vorherigen Betrachtung hinsichtlich der tatsächlichen Aussagekraft der vorab festzulegenden Stichprobe. Dasselbe gilt für stichprobenartig durchgeführte Besuche an Studienzentren als

Qualitätskontrollmaßnahmen in Anlehnung an Standards in klinischen Prüfungen.

Hierbei gilt es sorgfältig abzuwägen, inwieweit diese Maßnahmen geeignet sind, den Grundsatz der Nicht-Intervention in NIS/AWB zu gefährden, wie dies bereits 1996 von A. Koch, J. Windeler und U. Abel 1996 [19] aufgegriffen und diskutiert wurde.

Schlussfolgerungen

Der vfa repräsentiert mit seinen Mitgliedsunternehmen und deren Tochter- und Schwesterfirmen mehr als zwei Drittel des deutschen Arzneimittelmarktes und den Großteil der Forschungsaktivitäten im Arzneimittelsektor. Die dieser Umfrage zugrunde liegenden Antworten und Daten stammen aus den pharmazeutischen Unternehmen, die sowohl hinsichtlich ihrer Forschungstätigkeiten in den großen Therapie- und Indikationsgebieten wie auch bezogen auf ihre Unternehmensgröße zu den führenden Unternehmen in Deutschland zählen.

Zusammen mit den Empfehlungen der Bundesoberbehörden stellen die Empfehlungen der pharmazeutischen Verbände Vorgaben für Qualitätsstandards in nicht-interventionellen Studien mit Arzneimitteln zur Verfügung, die sich denen in klinischen Prüfungen annähern und damit ein hohes Maß an Vertrauen in die Qualität und Validität der Daten und der Ergebnisse rechtfertigen.

Anmerkungen

Interessenkonflikte

Die Autoren sind Mitarbeiter von VFA-Mitgliedsunternehmen.

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Zusammenfassung

Epidemiologische Studien sind nach der Erlangung der behördlichen Zulassung für ein neues Arzneimittel anerkannte, medizinisch wissenschaftliche Untersuchungsmethoden, die dem zusätzlichen Erkenntnisgewinn bei der routinemäßigen Anwendung des Medikamentes im klinischen Alltag dienen. Die Durchführung solcher Untersuchungen erfolgt gemäß den Empfehlungen der internationalen wie nationalen Fachgesellschaften, den Empfehlungen der Bundesoberbehörden in Deutschland sowie den Empfehlungen der Verbände der pharmazeutischen Industrie.

In zwei Umfragen unter den Mitgliedsunternehmen des Verbandes der forschenden Pharma-Unternehmen wurde der Stand der Umsetzung der Inhalte dieser Empfehlungen in den Jahren 2008 und 2010 untersucht und die Ergebnisse miteinander verglichen.

Es konnte gezeigt werden, dass diese Vorgaben erfolgreich umgesetzt und bei der Durchführung nicht-interventioneller Studien in Deutschland umfänglich berücksichtigt werden. Diese Empfehlungen definieren einen Qualitätsstandard, der ein hohes Maß an Vertrauen in die Validität der erhobenen Daten und die Ergebnisse aus diesen Untersuchungen rechtfertigt.

Schlüsselwörter: nicht-interventionelle Studien, Anwendungsbeobachtungen, Qualitätssicherung, qualitätssichernde Maßnahmen

Maxillary sinus augmentation using vertical bone condensing technique

Gagig Hakobyan, Anna Khachatryan

Introduction

Treatment of the fully or partially edentulous dentition with dental implants is a commonly and successfully used modality, showing a reliable long-term prognosis. Although this type of treatment leads to functionally predictable and esthetically pleasant results, the comparatively long treatment duration resulting from long healing periods is a major drawback. 1. After tooth loss, the periosteum of the maxillary sinus can exhibit increased osteoclastic activity, which can cause bone resorption. Alveolar bone loss that calls for elevation of the sinus floor to generate sufficient bone volume for implants at least 10 mm long can be categorized by the following: (1) an alveolar ridge of 5 to 10 mm, (2) an alveolar ridge equal to or less than 5 mm, and (3) a complete absence of alveolar bone between the sinus floor and alveolar crest. The first category is the most common and often permits simultaneous floor elevation and implantation. Implant placement in the atrophied maxillary posterior ridge with inadequate height of bone to restore masticatory function has always been difficult and challenging for clinicians. In the past few years, much attention and effort have been paid to developing a surgical technique to overcome this problem. Alveolar bone augmentation techniques include different surgical approaches such as guided bone regeneration, onlay grafting, interpositional grafting, ridge splitting and socket preservation. The sinus floor augmentation or elevation is a surgical technique that helps to resolve the problem of deficient bone height in the posterior maxillary region to receive the implants.3. The surgical technique currently used to augment the sinus floor to place the implant is either the lateral window opening or the osteotome technique.

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The procedures for sinus elevation for dental implant placement are as follows:

• The 2-stage lateral approach: The first stage entails sinus elevation and augmentation, and the second stage entails

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implant placement 6 to 9 months later. This is indicated when the bone height on the sinus floor is less than 4 mm.
• The 1-stage lateral approach: The dental implant is placed simultaneously with sinus elevation and augmentation. This is indicated when the bone height is 4 to 6 mm.
• The osteotome technique or crestal approach: Implants are placed at the same time that the sinus floor is locally augmented.This is indicated when the bone height is more than 5 to 8 mm.
Sinus floor augmentation with autogenous bone grafting for implant placement was first described by Boyne and James 2. In 1970, Tatum developed the method of antral floor grafting, based on a modified Caldwell-Luc lateral approach to the antrum, through the creation of a window in the maxillary bone.9. In 1980, Misch performed an augmentation of the sinus with simultaneous implant placement.11,12. Today the modified Caldwell-Luc approach is the most generally accepted method, allowing for the benefit of ready access to the sinus, significant elevation of the floor, and thus creation of sufficient bone volume to support the placement of implants. Another benefit of this method is the broad surgical field visibility it provides. The disadvantages of this technique are the relatively large surgical operation required, need for specialized instrumentation, risk of perforation of the schneiderian membrane, postoperational symptoms, and cost. Summers was the first to suggest the crestal approach osteotomy technique for sinus floor elevation.6-7. The lateral window opening is a more invasive and extensive procedure compared with the osteotome technique. As a result, more complications can be expected in the former technique. In a recent study, Schwartz-Arad et al reported 44% membrane perforation in 81 sinuses operated on by the lateral window opening technique.8. They also found that surgical complications did not significantly influence the implant survival. On the other hand, the osteotome technique seems to be easier to perform, with the possibility of fewer surgical complications. The osteotome sinus-floor elevation was proposed for implant sites with at least 5 mm to 8 mm of bone between the alveolar crest and the maxillary sinus floor and mainly in soft or poor quality, as is often encountered in the posterior maxilla.
The objective of our study was to assess the safety and efficacy of minimally invasive sinus floor elevation followed by bone augmentation and implant fixation.

Materials and methods

This study presents the efficacy of using vertical bone condensing technique with bone grafting in 38 patients during maxillary sinus-floor elevation procedure. Patient age ranged from 30 to 63 years, with an average of 53.4 years. Patients presented good oral health and no active periodontal disease, and only 4 were smokers. A total of 57 screw titanium dental implants were placed. All patients needed sinus floor elevation (5 of them bilaterally) because overall lateral alveolar bone height was less than 8 mm (vertical bone height). Presurgical radiographic evaluation is used to determine the severity of ridge resorption (CT, panoramic, and periapical radiograms). The patients should receive a detailed explanation regarding the technique and sign an informed consent prior to the procedure. Forty-six implants were placed by a 1-stage procedure at the time of reconstructive surgery. Eleven implants required a 2-stage procedure (first stage: grafting; second stage: placement of the implants) because less than 4 mm of bone height at the most inferior point of the maxillary sinus was conserved, and the residual original bone of the alveolar crest was not adequate to obtain primary implant stability. In this latter technique, the sinus floor is grafted through a small canal or hole to build up enough bone (>5 mm) in the first stage to provide implant primary stabilization for the second stage. In the second stage, the same area is regrafted, if necessary, and simultaneously the implant is placed. Patients were instructed to wash the mouth with chlorhexidine 0.2% twice daily, continue antibiotic therapy for 7 days. Loading of implants was performed after a mean time of 4.4 months after insertion, consisting of 4.0 months after a staged procedure or 5.2 months after a simultaneous procedure.

Results

Clinical and radiological follow-up examinations were performed immediately after the surgery, 3 months later, and every 6 months thereafter for the next 5 years. Radiographical analysis was performed by single-tooth X-rays and panoramic radiographs. No clinical signs of sinus pathology were observed, and no patients showed any sign of maxillary sinusitis. The clinical parameters evaluated were bleeding on probing and probing depth. Six months after surgery, the radiograph analysis confirmed a postgrafting opacity of the maxillary sinus floor in all patients. Vertical peri-implant bone levels were studied, too, at different times at the mesial and distal aspect of each implant. The aim was to calculate the vertical bone levels or the distance in millimeters from the implant shoulder to the first crestal bone to implant contact and the vertical bone loss 5 years after functional loading. Marginal bone loss around the implants was within established limits.

Conclusions

Endosseous-implant placement using a bone-condensing-and-expansion technique is not new, and several studies have shown excellent bone response as well as implant survival using osteotomes for placement of dental implants in the maxilla. 10,13,14,15,16.17. In a multicenter study, this technique has shown success rates as high as 96%. Osteotome sinus floor augmentation is a simple and conservative technique to increase the bone height on the sinus floor. The osteotome sinus-floor elevation technique increases new bone formation and leads to an enhanced osseointegration of dental implants in trabecular bone. The grafted area apical to the implant undergoes shrinkage and remodelling, the sinus floor boundary is eventually consolidated and replaced by newly formed cortical plate. Our clinical observations also showed no complications or patient discomfort. The soft sinus floor elevation technique represents a substantially less-invasive alternative for predictable implant installation in maxilla.

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Characteristic odour in the blood reveals ovarian carcinoma

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Abstract

Background

Ovarian carcinoma represents about 4% of all cancers diagnosed in women worldwide. Mortality rate is high, over 50%, mainly due to late diagnosis. Currently there are no acceptable screening techniques available, although ovarian cancer belongs to the group of malignancies for which mortality could be dramatically reduced by early diagnosis.
In a recently published study, we clearly demonstrated that human ovarian carcinoma tissues can be characterized by a specific odour, detectable by a trained dog. Another recent study confirmed these results using an electronic nose.

Methods

In the present work, we examined whether the cancer-specific odour can also be found in the blood. Two specially trained dogs were used. Both ovarian cancer tissues and blood from patients with ovarian carcinoma were tested.

Results

The tissue tests showed sensitivity of 100% and specificity of 95%, while the blood tests showed sensitivity of 100% and specificity of 98%.

Conclusions

The present study strongly suggests that the characteristic odour emitted by ovarian cancer samples is also present in blood (plasma) taken from patients with the disease. This finding opens possibilities for future screening of healthy populations for early diagnosis of ovarian carcinoma. A future challenge is to develop a sensitive electronic nose for screening of ovarian carcinoma by testing the blood/plasma to detect the disease at a stage early enough for treatment to be effective.

Background

Worldwide, there are more than 204,000 new cases of ovarian cancer annually, accounting for around 4% of all cancers diagnosed in women. Incidence rates vary considerably, with the highest rates in the United States and Northern Europe and the lowest rates in Africa and Asia. Around 43,000 cases occur each year in Europe, and 22,000 in the USA. In Sweden, the disease represents 3.1% of all cancer cases in women, totalling about 900 cases per year. Despite this relatively low incidence rate, it is the fifth most common cause of cancer death in women.
Because of the high mortality rates, ovarian cancer is one of several diseases that fulfil some of the criteria necessary for the introduction of population screening: it is an important

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health problem, and early detection is associated with improved outcomes. Potential screening tests for ovarian cancer have not yet been shown to reduce mortality, although both ultrasound and tumour markers can detect a significant proportion of ovarian cancers preclinically. Currently, there is no accepted screening programme for ovarian cancer [1-3].

In a recently published study, we clearly demonstrated that human ovarian carcinoma tissues can be characterized by a specific odour, detectable by a trained dog. The same study showed that a dog can be trained to distinguish between different histopathological types and grades of ovarian carcinomas, including borderline tumours, as well as different healthy control samples[4]. Double-blind tests showed 100% sensitivity and 97.5% specificity. Moreover, the odour of ovarian carcinomas seems to differ from those of other gynaecological malignancies, such as cervical, endometrial, and vulvar carcinomas, suggesting that different malignancies have different odour characteristics. The study further showed that early-stage and low-grade ovarian carcinomas emit the same specific smell as advanced tumours. These results suggest that the specific cancer odour may be used for screening, early diagnosis, and differential diagnosis of different malignant diseases in the future, when it becomes technologically possible.

Detection of other malignancies by dogs, such as melanoma [5] and bladder[6], breast, and lung cancer[7], has also been reported in peer-reviewed scientific journals.

Besides dog studies, different technical methods such as gas chromatography and mass spectrometry (GC/MS),[8] gas chromatography (GC)-based arrays,[9] and nanoparticle-polymer sensor arrays[10] have been used to detect malignant cells in vitro.

In our last study [11], volatile signals emitted by human seropapillary ovarian carcinoma samples and healthy tissues such as fallopian tube, myometrium, and postmenopausal ovarium were analyzed using an electronic nose. The electronic nose correctly classified 84.4% of cancerous tissues and 86.8% of the control material. These results confirm the basic results from our dog study; that is, the ovarian cancer samples emit specific odour/volatile signals. Although the study was small, the results offer some indication that early electronic detection of ovarian carcinoma may be possible.

One important challenge in this line of cancer research is to find suitable target(s) for diagnostic use; the blood offers a possible option.

The aim of this study was to test whether the specific odour emitted by ovarian carcinomas and borderline ovarian tumours can be detected by trained dogs in blood from patients with these diseases.

Methods

The dogs

Two dogs were used: Hanna, a 7-year-old black Giant Schnauzer (chip no. 967000000389928), and Lotti, a 3-year-old black Giant Schnauzer (chip no. 098100311386). Hanna was previously trained to detect ovarian carcinoma samples, and the test results were published in 2008[4]. In the present study, she was trained over the course of 9 months to detect blood samples from ovarian carcinoma patients, and during this time she did not sniff carcinoma samples. Lotti, who had not previously been trained, was trained during the same time period to detect ovarian carcinoma samples. Lotti had never sniffed blood samples before the test series.

Training

The training method is described in detail elsewhere;[4] a brief overview is given below.

Learning odour signature

Training was initially designed as a selection model, resembling the training of sniffer dogs. In brief, the dog was encouraged to sniff a few rags attached to pieces of string and placed on the floor. One of them contained an ovarian cancer sample. When the dog showed interest in the target, the handler quickly snatched it away. This was repeated several times.

Learning odour discrimination

When the dog was capable of identifying even low concentrations of the target vapour (finding the hidden tumour), we began using non-target odours as controls. Target and non-target samples were placed in glass containers, which were covered with perforated lids and placed inside wooden boxes (25 cm × 25 cm × 25 cm). The boxes and containers were cleaned with 95% alcohol after each run. We initially used only one control specimen, and the dog was permitted to choose the right parcel and disregard the control. Step by step, we increased the number of control samples to five (the combination of five controls and one target was considered a run). To minimize external influence, the exercises were carried out in several training rooms in random sequence.

Learning to distinguish extraneous odours

Although target and control samples were handled carefully in this phase of the training, other components such as boxes and glass containers were contaminated by different individuals, including the handler. However, this contamination had no observable influence on the dog's target identification during this last period of training.

Tumour and blood samples

Ovarian carcinoma samples consisting of different histopathological types of various grades and stages, including borderline tumours, were used during the training period[4]. Tumour material was collected at primary surgery, before chemotherapy. It was taken from the primary tumour in the pelvis (from the ovarium if possible, at early stages) but not from the peritoneum. All tumours were assessed by the same pathologist in accordance with regional treatment guidelines for gynaecological malignancies in western Sweden. The tumour samples were stored in small plastic tubes, preserved immediately at -20°C, and transported to our tumour bank (Ethical Committee license number: S-154-02), where they were kept at -80°C. Each tumour was divided into 10-30 samples of about 3 mm × 3 mm × 3 mm, and thawed at room temperature for 15-30 minutes before being used in the training. For the test sections, other gynaecological tumour samples, such as cervical, vulvar, and endometrial carcinomas, were also taken from this tumour bank and treated identically to the ovarian carcinomas. Sample imprints for cytological examination were performed on all tumours and all controls. The imprints were examined to verify the presence of malignancy (established when at least 75% of cells were malignant). Controls were accepted

Table 1. Calculated sensitivity and specificity

Dog indication	Cancer	Control	Sample
positive	a	b	a + b
Negative	c	d	c + d
	a + c	b + d	n

Sensitivity = a/(a + c), and specificity = d/(b + d).

Table 2. Dog's responses in Section 1 (Dog: Lotti; Material: tissues)

Box 1	2	3	4	5	6
Corp58	Myoma	Myoma	1786	Myoma	V
Corp58	Myoma	Fat	Myoma	285	V
Corp58	443	Myoma	Myoma	Ov	V
Corp58	Myoma	5377	Myoma	Myoma	Fat
425	Fat	Corp58	Myoma	Myoma	V
Myoma	Myoma	Coll2	270	Fat	Myoma
Myoma	Ov	Corp73	V	Myoma	5005
Fat	5011	Corp58	Fat	Myoma	Myoma
Myoma	Myoma	Corp73	Fat	5039	Ov
Myoma	Fat	466	V	Fat	Myoma

xxxx = target

Corp = endometrial carcionoma; Coll = Cervical carcinoma; V = vulvar carcinoma; Myoma = muscle from uterine walls (healthy individuals); Fat = abdominal, intraperitoneal fats from healthy individuals; Ov = healthy postmenopausal ovarium samples

Dog's responses:

Positive (bold)

Negative (monospace)

only in the complete absence of malignant cells.

Blood samples were obtained before primary surgery from patients with ovarian carcinoma and from patients with cervical, vulvar, and endometrial carcinomas. These samples were taken in EDTA tubes, then centrifuged at 3000 rpm for 10 min. and plasma pots over the small plastic tubes. The rest of the plasma samples after undergoing CA-125 analysis, were kept at -80°C in our tumour bank (Ethical Committee license number: S-220-08). Blood samples with >500 IU CA-125 values were used for training, with one drop being placed in a small plastic dish inside each box.

Table 3. Clinicopathological features in Section 1 (Dog: Lotti; Material:tissues)

Tissue	CA-125 U/ml	Histology	Grade	Stage	Diagnosis
1786	> 200	seropapillary	2	III/C	Ca. ovari
285	< 35	mucinous		III	Borderline
443	500	seropapillary	3	III/C	Ca. ovari
5377	100	mucinous	1	I/A	Ca. ovari
425	154	serous		III/A	Borderline
270	180	carcinosarcoma		III/B	Ca. ovari
5005	< 35	endometroid	1	I/B	Ca. ovari
5011	80	endometroid	3	II/B	Ca. ovari
5039	195	carcinosarcoma		II/B	Ca. ovari
466	-	mucinous	3	III/B	Ca. ovari
V	< 35	squamous	2	II	Ca. vulvae
Corp58	< 35	endometroid	3	II/A	Ca. corp. ut.
Corp73	< 35	endometroid	2	I/B	Ca. corp. ut.
Coll2	< 35	squamous	3	III/A	Ca. colli ut.

Table 4. Dog's responses in Section 2 (Dog: Hanna; Material: plasma)

Box 1	2	3	4	5	6
V	8783	Corp1	XX	Coll	XX
V	X	Corp1	XX	Coll	3622
V	XX	X	1200	Corp1	XX
3712	X	Corp2	V	Coll	XX
Coll	XX	Corp1	V	3607	X
Coll	XX	2246	V	Corp1	Corp2
3609	X	Coll	V	Corp2	XX
XX	XX	Coll	V	Corp2	2124
X	2192	Coll	XX	Corp2	XX
XX	Corp2	Coll	V	3654	XX

xxxx= target

V = vulvar carcinoma; Coll = cervical carcinoma; Corp = endometrial carcinoma; × = plasma obtained from healthy female individuals; XX = plasma obtained from healthy male individuals

Responses:

Positive (bold)

Negative (monospace)

Median donor age was 67 years (range: 35-79) for tissue samples and 63 years (range: 45-77) for blood samples. Tissue and blood samples used during the training period were not used in the tests.

Controls

Abdominal fat and muscle (myomas), and healthy postmenopausal ovarium samples were used as controls. Control blood (plasma) samples were collected from young, healthy female individuals. However, in some cases we also used blood samples from male individuals, including handlers. This had no observable influence on the dog's target identification. Control plasma samples were treated identically to the targets. Median donor age was 65 years (range: 40-81) for tissue samples and 41 years (range: 27-67) for blood samples. Tissues and blood samples used during

Table 5. Clinicopathological features in Section 2 (Dog: Hanna; Material: plasma)

Plasma	CA-125	Histology		Stage	Diagnosis
8783	< 35	mucinous		I/A	Borderline
3622	< 35	endometroid	3	III/B	Ca. ovari
1200	> 500	seropapillary	2	III/B	Ca. ovari
3712	< 35	mucinous		II/B	Borderline
3607	< 35	seropapillary	3	III/C	Ca. ovari
2246	> 100	seropapillary	2	III/C	Ca. ovari
3609	< 35	adenocarcinoma	2	I/B	Ca. ovari
2124	> 500	seropapillary	3	III/C	Ca. ovari
2192	> 500	seropapillary	2	III/A	Ca. ovari
3654	< 35	adenocarcinom	3	IV	Ca. ovari
Vulva	< 35	squamous	2	II	Ca. vulvae
Corp 1	< 35	endometroid	3	I/C	Ca. corp. ut.
Corp 2	< 35	endometroid	3	I/C	Ca. corp. ut.
Coll	< 35	adenocarcinoma	2	II/A	Ca. colli ut.

Table 6. Dog's responses in Section 3 (Dog: Lotti; Material: plasma)

Box 1	2	3	4	5	6
V	X	Corp1	X	Coll	2124
X	XX	3646	X	Corp1	Coll
7673	XX	V	X	Coll	Corp1
Coll	X	V	XX	2192	Corp1
Coll	6647	X	XX	X	Corp1
Coll	Corp2	V	X	XX	3631
X	Corp2	V	2139	X	X
3657	Corp1	X	Coll	XX	XX
XX	X	Corp1	Coll	2144	X
XX	Corp2	3635	Coll	V	X

xxxx = target
V = vulvar carvinoma; Coll = cervical carcinoma; Corp = endometrial carcinoma; × = plasma
obtained from healthy female individuals; XX = plasma, obtained from healthy male individuals
Responses:
Positive (bold)
Negative (monospace)

the training period were not used in the tests.

Test design

Tests were carried out according to the double-blind principle; both test leader and handler were blinded to the location of the target samples, and were present in the test location only when the dogs were working. The dogs were tested in four sections, two on day 1 and two on day 2. Each section was composed of ten runs, and each run included six boxes; five of the boxes contained control materials and the remaining box contained the target material. Placement of the target box was changed by an outside assistant between each run. Section 1 (day 1): Lotti sniffed tissues; Section 2 (day 1): Hanna sniffed blood; Section 3 (day 2): Lotti sniffed blood; Section 4 (day 2): Hanna sniffed tissues. The tests were documented on paper and DVD.

Dog's response

A positive response was defined as indicating the target box by scratching with foreleg(s) and lying down or sniffing at,

Table 7. Clinicopathological features in Section 3 (Dog: Lotti; Material: plasma)

Plasma	CA-125	Histology	Grade	Stage
2124	> 500	seropapillary	3	III/C
3646	< 35	endometroid	2	III/B
7673	< 35	mucinous	--	I/C
2192	> 500	seropapillary	2	III/A
6647	< 35	mucinous	-	I/B
3631	< 35	seropapillary	2	III/B
2139	> 200	carcinosarcom	-	III/A
3657	< 35	seropapillary	1	III/C
2144	> 500	adenocarcinoma	3	II/A
3635	< 35	seropapillary	3	III/B
Vulva	< 35	squamous	2	II
Corp 1	< 35	endometroid	3	I/C
Corp 2	< 35	endometroid	3	I/C
Coll	< 35	adenocarcinoma	2	II/A

Table 8. Dog's responses in Section 4 (Dog: Hanna; Material: tissues)

Box 1	2	3	4	5	6
Fat	258	Myoma	V	Corp	V
Corp58	Myoma	Fat	Myoma	Corp	1786
5005	Fat	Myoma	Myoma	Ov	V
Corp58	Myoma	Fat	5039	Myoma	Fat
V	Fat	Fat	Fat	Corp	147
Fat	V	425	V	Fat	Fat
Myoma	5011	Fat	Fat	Corp73	Fat
V	Corp58	Corp58	Fat	270	Myoma
5377	Myoma	Corp73	Fat	V	Ov
Myoma	Fat	Fat	443	Fat	Myoma

xxxx = target
Corp = endometrial carcinoma; Coll = Cervical carcinoma; V = Vulvar carcinoma; Myoma = muscle from uterine walls (healthy individuals); Fat = abdominal, intraperitoneal fats from healthy individuals; Ov = healthy postmenopausal ovarium samples
Dog's responses:
Positive (bold)
Negative (monospace)

but not indicating the control samples. A negative response was defined as indicating a control box and not indicating the target.

Statistical methods

Sensitivity and specificity were calculated in the same way as for diagnostic testing. That is, the sensitivity (or the true positive rate) of the test was the proportion of cancer samples that were correctly identified by the dog, and the specificity (or the true negative rate) was the proportion of control samples negatively indicated by the dog.
Binomial probability distribution was used to compare the performance of the dog with a random selection of sample boxes. Each test consisted of ten runs, each of which included one target sample and five controls. Under the assumption

Table 9. Clinicopathological features in Section 4 (Dog: Hanna; Material: tissues)

Tissue	CA-125 U/ml	Histology	Grade	Stage	Diagnosis
1786	> 200	seropapillary	2	III/C	Ca. ovari
285	< 35	mucinous		III	Borderline
443	500	seropapillary	3	III/C	Ca. ovari
5377	100	mucinous	1	I/A	Ca. ovari
425	154	serous		III/A	Borderline
270	180	carcinosarcoma		III/B	Ca. ovari
5005	< 35	endometroid	1	I/B	Ca. ovari
5011	80	endometroid	3	II/B	Ca. ovari
5039	195	carcinosarcoma		II/B	Ca. ovari
147	-	mucinous	3	II/B	Ca. ovari
V	< 35	squamous	2	II	Ca. vulvae
Corp58	< 35	endometroid	3	II/A	Ca. corp. ut.
Corp73	< 35	endometroid	2	I/B	Ca. corp. ut.
Coll2	< 35	squamous	3	III/A	Ca. colli ut.

of random positive indication by the dog, the number of correctly identified runs was a binomial distribution with a 1/6 probability of success (Table 1).

Results and Discussion

Section 1: The dog correctly identified all cancer samples, giving a sensitivity of 100%. Two controls out of 50 were indicated, giving a specificity of 96% (Tables 2 and 3).

The probability of the dog getting at least 8 out of 10 runs completely correct entirely by chance (assuming the two indicated controls belonged to different runs) was 8.43*10-7.

Section 2: The dog correctly identified all plasma samples, both from cancer patients and healthy controls, giving sensitivity and specificity of 100% (Tables 4 and 5).

The probability of the dog getting all 10 runs completely correct entirely by chance was 1.65*10-8.

Section 3: The dog correctly identified all plasma samples taken from patients with ovarian carcinoma (sensitivity = 100%), and also indicated two out of 50 control samples, giving a specificity of 96% (Tables 6 and 7).

The probability of the dog getting at least 8 out of 10 runs completely correct entirely by chance (assuming the two indicated controls belonged to different runs) was 8.43*10-7.

Section 4: The sensitivity was again 100%, and the dog indicated 3 out of 50 control tissues including other gynaecological carcinomas, giving a specificity of 94% (Tables 8 and 9).

The probability of the dog getting at least 7 out of 10 runs completely correct entirely by chance (assuming the three indicated controls belonged to different runs) was 1.94*10-5.

When the results were pooled by sample type, the tissue tests showed a sensitivity of 100% and a specificity of 95%, and the plasma tests showed a sensitivity of 100% and a specificity of 98%.

This study is the first presentation of a specific odour emitted by human plasma from ovarian cancer patients. In addition, it reveals the important observation that trained dogs can discriminate between plasma samples from ovarian cancer patients and plasma taken from patients with other malignancies such as endometrial, cervical, and vulvar carcinomas.

The present study also confirms results from our previous work, in which we showed that a trained dog could discriminate different histopathological types and grades of ovarian carcinoma tissues, including borderline tumours, from healthy control samples including postmenopausal ovary. The dog could also discriminate ovarian carcinoma tissues from all other gynaecological malignancies. Sensitivity and specificity rates in the double-blind test series were 100% and 97.5%, respectively[4]. In the present study, the sensitivity and specificity for the two tissue tests (Sections 1 and 4) were 100% 95%, respectively.

The present study strongly suggests that the characteristic odour emitted by ovarian cancer samples is also present in blood (plasma) taken from patients with the disease. This observation suggests that the specific cancer odour in the blood/plasma may be used for screening, diagnosis, and differential diagnosis of different malignant diseases. The past decade has seen an increasing amount of research into different technical methods of identifying the characteristic volatile organic compound (VOC) signals emitted by malignancies. Methods such as gas chromatography and mass spectrometry,[8] gas chromatography-based arrays,[9] and nanoparticle-polymer sensor arrays[10]-"chemical noses" and electronic noses-have been used to detect malignant cells in vitro, and diagnostic methods for lung cancer using exhaled breath have also been investigated[12].

Our recently completed study presents the first evidence that an electronic nose can provide an easy technique to distinguish the VOC signals emitted by human ovarian carcinomas and healthy human fallopian tube, myometrium, and postmenopausal ovary, respectively[11]. The electronic nose showed a sensitivity of 84.4% and a specificity of 86.8% in the total material. However, in that study we did not test our electronic nose on blood/plasma samples or on malignancies other than ovarian carcinoma.

It is not easy to make comparisons between the present study and other dog studies. Two of the available dog studies used training methods that differed from those in the present study, as well as different target materials [6,7]. A third study was, like ours, based on tissue material, but included only a very limited number of tissues [5].

Our observations from dog studies show that trained dogs can detect even as small a quantity as 20 ovarian carcinoma cells on the abdominal fat (data not shown). Thus, the cancer-specific odour/VOC components are emitted even in early phases of tumour development. We believe that a significant challenge for future experiments is to construct more sensitive electronic noses, not only for early detection but also for differential diagnosis between malignancies. If the electronic nose is to be used for screening of ovarian carcinoma by testing the blood/plasma, it must be able to detect the disease in the early stages, when treatment is effective.

It is difficult to compare the sensitivity of a dog's nose to that of the electronic nose. Dogs detect only odour molecules, whereas electronic noses may also detect several odourless compounds (e.g. CH4). The two systems may thus detect different levels of sensitivity. Our experience suggests that trained dogs could be used under controlled circumstances in experiments as complementary "instruments" to further explore this very interesting new property of malignancies. Similar suggestions were published by Gordon et al. [13].

Conclusion

The present study strongly suggests that the characteristic odour emitted by ovarian cancer samples is also present in blood (plasma) taken from patients with the disease.

Financial and competing interests

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The figures and tables presented here are original and have

not been presented earlier.

Authors' contributions

GH: project leader, study design, dog training and handling, coordination of manuscript drafting; HA: collecting blood samples statistical calculations required for the study design, drafting part of the manuscript; GP: collecting tissues (some, which lacking in the tumour bank), drafting part of the manuscript, participating in the study coordination. All authors read and approved the final manuscript.

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Condition of the oxidative metabolism of erythrocytes under the influence of finely dispersed aerosols of polymetallic dust and alimentary correction

Lyazat K. Ibrayeva

Sensitive indicator of reaction of an organism on influence industrial and environment are condition changes свободнорадикального oxidations. As a result of various toxic influence there is a control failure over processes липопероксидации that leads to easing of barrier function and increase in permeability of biomembranes [1]. The system антиоксидантной organism protection provides linkage and updating of radicals, the prevention of formation or destruction of peroxides [2].

Materials and research methods.

Experiment on white rats-males with weight 180-200 gram has been made. For dusting the fraction of dust aerosols of a polymetallic dust from a 55th mines of the city of Satpaev was selected. The structure of a polymetallic dust included 53,7 % of a free dioxide of silicon, 8 % of copper, 0,04 % of arsenic, 0,003 % of antimony and 3 % of the titan. By finely dispersed aerosols of a polymetallic dust the dynamic inhalation priming of rats was spent to concentration of 10 mg/m3 in bare chambers for 4 hours per day of 5 days per week by means of the device developed by us (the

The national center for occupational hygiene and occupational diseases, Karaganda, Kazakhstan.

innovative patent №23391 from 12/15/2010 «the Device for an inhalation priming of experimental animals polymetallic dust»).

For alimentary correction of dust influence on an organism taking into account main principles of correction the specialized product of "Adapt-Lang" (the patent for the invention №17191 from 5/11/2004 «Means for increase of stability of an organism to fibrogenic to dust action») has been developed and approved in experimental model. The offered structure represents the combined complex of products of the vegetative and animal origin, raising nonspecific resistance of an organism to influence of technogenic factors. Means not toxically, successfully connects and deduces alien substances from an organism.

The specialized product of "Adapt-Lang" was applied as an additional component of a food to traditional diet to the experimental rats, for the purpose of correction in a dose which was not exceeding 1/10 daily doses of food. All experimental rats received food with power value of 95,9 kcal. The diet was made according to the standard specifications [3].

Rats shared on 4 groups: 1 – control (intact rats receiving total diet), 2 group – dusting by finely dispersed aerosols of polymetallic dust, receiving total diet, 3 group – "Adapt-Lang" receiving a specialized product in parallel diet on the background of dusty by finely dispersed aerosols of polymetallic dust.

Experiment terms made 40, 90 and 180 days that corresponded to 5 years, 10 years and 20 years of the experience of work of the person in dust conditions [4].

After term of experiment animals were killed by instant euthanasia method . In red blood defined a condition of an oxidizing metabolism in hemilyuminometre with use of the applied computer program Lab Graphic System, developed by Sokolovsky C and Fedorovym A [5]. Statistical processing of an analyzed material was spent with use of a package of applied programs «Statistika 5.0». Calculation of factor of reliability (P) which was estimated under the table of values of criterion (t) on Syudent [6-9] was carried out.

Results of own researches.

Imax in red blood at rats of 2 groups raised from 1 days of experiment on 57 % concerning control. By 40 days this indicator became in 2,2 times above, than for 3 days, and for 90 days - on 67 % above, than for 40 days. Tmax in erythrocytes of ruts of this group from 1 days of experiment was above control on 19 %, by 40 days it became still above on 35 %, than for 3 days, for 90 days above on 56 %, than for 40 days of experiment. Oppression antioxidant activity in erythrocytes occurred by 180 days of dusting to what decrease Tmax on 36 % in comparison with 90 days testifies.

Thus, at action of finely dispersed aerosols of a polymetallic dust by data of chemiluminescent method increase of the maximum value of intensity chemiluminescent, characterizing intensive formation of free radicals in erythrocytes already on early terms of experiment is revealed. It specifies in aggression of a polymetallic dust.

The indicator characterizing antioxidant activity of an organism, - time of an exit of a curve for a maximum testifies to its decrease in erythrocytes of blood only by 180 days of experiment.

In erythrocytes of rats of 3 groups decrease Imax for 40-90 days on 63-62 % and for 180 days of experiment on 51 % in comparison with 2 group was observed. Along with it there was reduction Tmax by 37-40 % by 40-90 days and its increase at 60 % at 180 days of experiment in comparison to 2 group.

Thus, at alimentary correction by means of a specialized product of "Adapt-Lang" on the background of dusty by finely dispersed aerosols of a polymetallic dust in erythrocytes of blood of rats intensity of free radical oxidations decreased and raised antioxodant activity.

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Entropy and time in living organisms

Ignat Ignatov

The second law of thermodynamics states that the entropy of any closed system always strives toward an increase, i.e. increase of chaos. In information theory, entropy is a measure for insufficiency of information in a physical system and is a function of probability. Entropy is infinite if probability is zero.

According to Hawking, the second law of thermodynamics defines that the states of chaos significantly outnumber the states of order. He makes the assumption that in the beginning a system has a small number of orderly states. Over time, this system develops according to natural laws and its states change. At later stages, the states of chaos increase in number. Eventually, its states of chaos increase and so does entropy. He uses as an example the computer's memory, which is based on the binary numeral system. The direction of time in which the computer saves the past is the same direction in which disorder increases.

Schrödinger demonstrates a correlation between the entropy of living organisms and the environment. Living organisms decrease their own entropy at the expense of the increase of the entropy of the environment.

Entropy is a measure of randomness or disorder of the physical system. It is expressed in the number of possible arrangements of the components. Prigozhin received the Nobel Prize explaining that at a statistical level the chaotic states of living systems lead to an irreversible behavior. Self-structuring and self-organization are observed. He explains the auto-oscillatory reaction of Belousov–Zhabotinsky. Prigozhin shows how together with the increase of entropy, self-organization originates.

According to the author, living organisms decrease their own entropy due to their orderliness. This orderliness increases with the transition from unicellular to multicellular organisms. Cells divide in a particular sequence. Living organisms live with their our own energy, and also exchange substances and energy with the environment. The environment increases its entropy and thus its disorder. Over time, the living organism has more and more difficulties to adapt. This adaptation depends on the consistency and velocity of life processes. Time is a fundamental concept in physics and philosophy and the fourth dimension in space – the time continuum. According to Einstein's theory of relativity, there are 3 spatial and one time dimension. Time measures the duration and sequence of states and events.

The more rapid the life processes, the faster the states of orderliness are observed, i.e. entropy decreases. Yet this leads to difficulties in compensating entropy with that of the environment, which is associated with metabolism and energy. These organisms such as mammals are able to live up to 100 years. In trees processes are slower, the states of orderliness are obtained more slowly and entropy decreases more slowly than in animals. In trees 'life' energy accumulates more slowly. There are trees that live more than 1000 years. For example in the turtle life processes are slower than in mammals and faster than in trees. It can live up to 300 years. For each living creature its own time can be defined, which somewhat differs from the time of the environment. This time correlates with parameters of the vital activity of living organisms (Ignatov, 2011).

When considering the origin of life, the question arises whether there is information in surrounding space for this event. The information in the electromagnetic spectrum spreads with the speed of light. The plant world has originated 1.5 billion years ago. The spectrum of reflected light from plants in the red diapason is interrupted. This means that if this information can be disseminated and there is a highly-sensitive apparatus at a distance of 1.5 billion light years, this apparatus at present time will monitor the process that has occurred on Earth 1.5 billion years ago.

Let us imagine that from the Earth there is information at 1 light year. This information is identical on a sphere with a radius of 1 light year. Any observer from this sphere sees different information compared to other observers. Yet each observer from the sphere observes the center in the same way. In this regard, in the electromagnetic spectrum there is no identical information in different points, if a center of the coordinate system for observation has not been marked. This is an illustration of how time and space are related, when information is disseminated at the speed of light. Light quanta or photons have no mass. The presence of mass leads to deceleration. The question remains how fast can living matter with mass move in space.

However, when we obtain information from living organisms, it is in the electromagnetic range. In some of them there are also acoustic waves.

But how does time from surrounding space affect living matter?

Here are two examples from Hawking. Let's observe an airplane that flies over a hilly area. Although it moves in a straight line in three-dimensional space, its shadow depicts a bent path on the two-dimensional earth surface. The mass of the Sun bends space-time as follows. When the Earth moves in a straight line in four-dimensional space-time, to us it seems that it moves in a circular orbit in three dimensional space. The general relativity theory of Einstein stipulates that in proximity to such a massive body like the Earth, time slows down. The development of life is a unique phenomenon and the lifetime of any living thing depends on the speed of its processes, the "vital" energy, which is a measure of entropy, and the exchange of energy and substances with the environment. Diseases are a violation of processes in the organism and they create chaos in the living organism, as well as a shorter lifetime (Ignatov, 2011).

This means that if an earth organism lives on another planet, a series of evolutionary changes will commence, related to gravity, light, water quality, etc. The organism's own time will change, due to the different entropy and time of the environment.

In 2010, I stated evidence that the origin of life depends both on the properties and structure of water and on additional

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http://www.medicalbiophysics.dir.bg/en/water_memory.html

conditions. Closest to these conditions, leaving a trace in plants with its structure and entropy, is mineral water, which reacts with calcium carbonate. Next in quality rank marine and mountain waters (Ignatov, 2010). This water is closest in its spectrum to the cactus juice as a model system. Therefore I have introduced the concept of "informativity" of water. Water has a number of unique properties that allow it to store and disseminate information as a result of external physical or chemical factors of influence. However, without this property of the water, one can hardly explain the origination of living matter, moreover in "chaotic" water (Dr. Ignatov, 2010). Water for origination of life reduces its own entropy compared to the water that has no characteristic peaks for living matter (Ignatov, 2011).

In the origination of life, Mosin states that the information properties of water have been better because of deuterium molecules in the water. In such water entropy declines faster. Living creatures are part of Nature and the discovery of new planets gives us a chance to also discover extraterrestrial life forms.

Long-term effect of metformin on blood glucose control in non-obese patients with type 2 diabetes mellitus

Hiroyuki Ito, Hidenori Ishida, Yuichiro Takeuchi, Shinichi Antoku, Mariko Abe, Mizuo Mifune and Michiko Togane*

Abstract

Background

We aimed to investigate the long-term effect of metformin on the blood glucose control in non-obese patients with type 2 diabetes mellitus.

Methods

A retrospective study was performed in 213 patients with type 2 diabetes mellitus under the administration of metformin for more than one year. The clinical parameters were investigated for 3 years. The obese and non-obese individuals were defined as a body mass index (BMI) of 25 kg/m^2 or over (n = 105) and a BMI of less than 25 kg/m^2 (n = 108), respectively.

Results

HbA1c levels were significantly decreased compared with those at the baseline time. The course of HbA1c was similar between the non-obese and the obese groups, while the dose of metformin required to control blood glucose was significantly lower in the non-obese group than in the obese group. The reductions in HbA1c were 1.2% and 1.1% at 12 months, 0.9% and 0.9% at 24 months, and 0.8% and 1.0% at 36 months in the non-obese and obese groups, respectively. BMI did not change during the observation periods. Approximately half of all patients required no additional antidiabetic agents or a reduction in other treatments after the initiation of metformin in either of the two groups.

Conclusions

The present study demonstrated the long-term beneficial effect of metformin in non-obese (BMI < 25 kg/m^2) diabetic patients. This effect appears to be maintained even after the observation period of this study, because metformin was limited to a relatively low dose in the non-obese group and the observed worsening in glycemic control over time can probably be attenuated by increasing the dose of metformin.

Background

Metformin, one of the biguanide agents, has been recommended for the treatment of patients with type 2 diabetes mellitus according to the consensus algorithm published by the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA), because it is economical, induces less weight gain and does not cause hypoglycemic attacks, in addition to its glucose-lowering effect [1] . The UK Prospective Diabetes Study (UKPDS) demonstrated that metformin is as effective as sulfonylurea to control the blood glucose levels of obese patients with type 2 diabetes mellitus. Metformin yielded a stable patient body weight, cardiovascular protection and a better patient survival rate compared with sulfonylurea or insulin therapy [2,3] . Therefore, metformin is now accepted as the first-line drug for the type 2 diabetic obese patients.

The body mass index (BMI) and body fat percent are different between Asians and Caucasians. The BMI is 3 - 4 units lower in the general population in Asian compared to Caucasians [4] . It is similar in Japanese diabetic patients, for example, the mean BMI was 22.9 kg/m^2 in men and 23.4 kg/m^2 in women in the Japan Diabetes Complications Study (JDCS), which was a nationwide multi-center prospective study of type 2 diabetic patients [5] . Therefore, the strategy for treating non-obese patients is considered to be important in the treatment of type 2 diabetes mellitus for Asians, including Japanese.

Although it has been reported that metformin is effective for non-obese diabetic individuals, the observation periods were relatively short, usually less than one year [6-12] .

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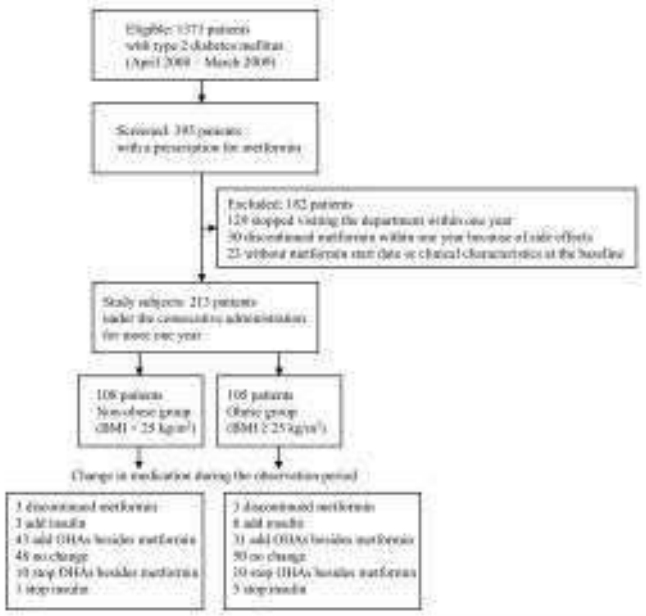

Figure 1. Flow diagram of the population cohort. BMI: body mass index. OHAs: oral hypoglycemic agents.

Because the effects of oral hypoglycemic agents (OHAs), including metformin, and insulin are gradually reduced as the treatment periods increase [2,13] , the observation of metformin over a longer duration is necessary.

In the current study, we aimed to investigate the long-term effects of metformin on blood glucose control in non-obese Japanese patients with type 2 diabetes mellitus.

Patients and Methods

Three hundred ninety-five subjects who received metformin were conducted to be eligible for this study among 1371 patients with type 2 diabetes mellitus being treated in the Department of Diabetes, Metabolism and Kidney Diseases of Edogawa Hospital, Tokyo, Japan between April 2008 and March 2009 (Figure 1). Any individuals who had stopped visiting our department by changing the hospital or for other unspecified reasons for less than 1 year (n = 129) or who discontinued metformin within 1 year after the initiation because of side effects (n = 30), such as gastrointestinal symptoms and liver injury, were excluded from this study. The patients with an uncertain metformin treatment start date or without clinical characteristics at the baseline (before initiating metformin therapy) time were also excluded from the present series (n = 23). Finally, a retrospective study was performed in a population of 213 patients with type 2 diabetes mellitus under the consecutive administration of metformin for more than 1 year. The clinical parameters, including BMI, HbA1c level and the history of medication were investigated from the baseline (the initial date of metformin therapy) for 3 years.

Figure 1. Flow diagram of the population cohort. BMI: body mass index. OHAs: oral hypoglycemic agents.

All of the indications, doses and discontinuation of metformin were guided by each patient's physician. Although the optimization of the treatment, such as a dose increase of metformin, an addition/reduction of the other OHAs and an introduction of insulin therapy, was also judged by the chief physician, it was performed if the HbA1c levels remained higher than 7% or less than 5.8% for 2-3 months [14] .

The obese and non-obese individuals were defined as having a BMI ≥ 25 kg/m^2 and a BMI < 25 kg/m^2, respectively. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg. The participants currently using antihypertensive medications were also classified as positive for hypertension. Serum total cholesterol, LDL-cholesterol, and HDL-cholesterol concentrations were measured with TBA-200 FR NEO using Determiner L TC II, Determiner L LDL-C, and Determiner L HDL-C instruments (Kyowa Medex Co., Ltd., Tokyo, Japan). Hyperlipidaemia was defined by serum concentrations of total cholesterol levels ≥5.7 mmol/L, LDL-cholesterol levels ≥ 3.6 mmol/L, or as patients who were already undergoing treatment with lipid-lowering agents. The triglyceride concentrations were not investigated in this study because fasting blood samples could not always be obtained for measurements. HbA1c levels were determined with a high performance liquid chromatography method using an automated HLC-723G7 analyzer (Tosoh Corporation, Tokyo, Japan) and calibrated by the Japan Diabetes Society (JDS) standard calibrators. The eGFR was calculated using the formula reported by Matsuo et al [15] . This equation originated from the MDRD study group [16] arranged for Japanese individuals, and it is recommended by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = $194 \times Scr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female).

Statistical analysis

An analysis of variance (ANOVA) and the χ^2 test were used

Table 1. Baseline characteristics of the patients

	Non-obese	Obese	
	(n = 108)	(n = 105)	P
Body mass index (kg/m^2)	22.7 ± 1.7	28.4 ± 2.9	<0.01
Age (years)	64 ± 7	59 ± 10	<0.01
Men (%)	49	52	0.63
Duration of diabetes mellitus (years)	12 ± 9	8 ± 7	<0.01
Current plus past smoking (%)	62	67	0.59
Current drinkers (%)	58	60	0.79
Therapeutic method for diabetes mellitus			
Diet only/OHAs/Insulin (%)	16/67/18	31/48/21	<0.01
Systolic blood pressure (mmHg)	132 ± 16	137 ± 16	0.01
Diastolic blood pressure (mmHg)	78 ± 10	81 ± 11	0.02
Hypertension (%)	61	87	<0.01
Total cholesterol (mmol/L)	5.3 ± 1.1	5.3 ± 1.1	0.71
LDL cholesterol (mmol/L)	2.9 ± 0.7	3.1 ± 0.8	<0.01
HDL cholesterol (mmol/L)	1.6 ± 0.5	1.4 ± 0.3	0.09
Hyperlipidaemia (%)	81	84	0.52
Haemoglobin A1c (%)	8.1 ± 2.0	8.1 ±1.7	0.90
Uric acid (μmol/L)	282 ± 84	302 ± 79	0.10
Serum creatinine (μmol/L)	67 ± 17	67 ± 15	0.71
Estimated GFR (mL/min/1.73 m)	72.6 ± 17.3	75.5 ± 17.7	0.25
Initial dose of metformin (mg/day)	556 ± 110	566 ± 116	0.49

OHAs: oral hypoglycemic agents, GFR: glomerular filtration rate

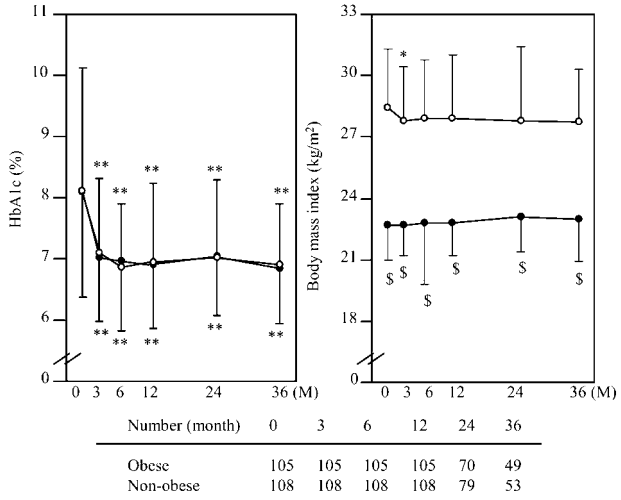

*Figure 2. Changes of HbA1c levels and body mass index in obese and non-obese patients with type 2 diabetes mellitus. Data represent the mean ± SD. Open and closed circles represent the values in obese and non-obese individuals, respectively. * P < 0.05 and ** P < 0.01 vs. 0 M (initiation of metformin). $ P < 0.01 vs. obese.*

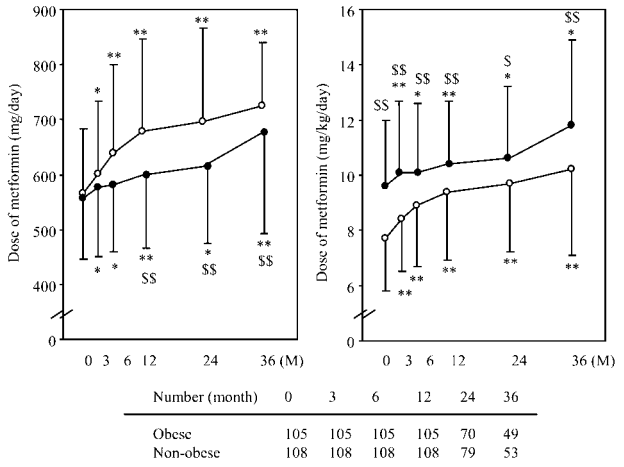

*Figure 3. Changes in the dose of metformin and those corrected by the patient's body weight. Data represent the mean ± SD. Open and closed circles represent the values in obese and non-obese individuals, respectively. * P < 0.05 and ** P < 0.01 vs. 0 M (initiation of metformin). $ P < 0.05 and $$ P < 0.01 vs. obese.*

for between-group comparisons of the continuous and categorical variables, respectively. A paired t-test was conducted to determine whether there were any differences in the dose of metformin, HbA1c levels or BMI during the observation period compared to the baseline values. Pearson's univariate regression was performed to determine whether there was any association of reduced HbA1c with other clinical parameters. The odds ratio (OR) and respective 95% confidence interval (95% CI) were determined to examine the strength of the relationship between the requirement of additional glucose-lowering agents (OHAs or insulin) and the clinical parameters based on a multiple logistic regression analysis. Differences with P-values of less than 0.05 (two-tailed) were considered to be statistically significant. The statistical software package JMP, version 8.0 (SAS Institute, Cary, NC, USA), was used to perform all of the analyses.

Results

Table 1 shows the baseline characteristics of the study patients. The age and the duration of diabetes mellitus were significantly higher and longer in the non-obese group than in the obese group. There was a greater frequency of patients without any antidiabetic agents prior to metformin administration in the obese group (31%) than in the non-obese group (16%). The blood pressure levels, the prevalence of hypertension and serum LDL-cholesterol concentrations were significantly higher in the obese patients than in the non-obese patients. The HbA1c levels and the initial dose of metformin were not different between the two groups.

During the observation period, HbA1c levels were significantly decreased compared with the baseline levels (Figure 2). The course of HbA1c was equal between the non-obese and the obese groups. HbA1c was reduced by 1.2% and 1.1% at 12 months, 0.9% and 0.9% at 24 months, 0.8% and 1.0% at 36 months in the non-obese and obese groups, respectively. Although the dose of metformin required to control the blood glucose levels gradually increased during the observation period (Figure 3), it was significantly lower

Table 2. HbA1c reduction determinants by correlation coefficient

	1 year		2 years		3 years	
	r	P	r	P	r	P
Sex	0.06	0.42	-0.07	0.42	-0.15	0.14
Age	0.11	0.60	-0.02	0.79	0.14	0.16
Duration of diabetes	0.24		0.16	0.10	0.15	0.21
Body mass index	-0.04	0.54	-0.04	0.61	-0.10	0.34
HbA1c at baseline	-0.81		-0.73		-0.82	
Hypertension	-0.09	0.19	-0.01	0.93	-0.01	0.91
Hyperlipidaemia	-0.02	0.75	-0.04	0.65	0.23	0.47
Estimated GFR	0.03	0.69	0.04	0.63	0.04	0.67
Therapeutic method	0.13	0.07	0.17	0.10	0.11	0.27
Initial dose of metformin	-0.11	0.11	0.01	0.94	-0.03	0.75
Metformin dose at 1 year	-0.07	0.32	0.08	0.36	-0.01	0.86

GFR: glomerular filtration rate. Sex (man = 1, woman = 2), therapeutic method (diet = 1, oral hypoglycemic agents = 2, insulin = 3), hypertension (absent = 0, present = 1) and hyperlipidaemia (absent = 0, present = 1) were replaced with a number.

Table 3. Odds ratios for the requirement of additional agents in the non-obese and obese patients with type 2 diabetes mellitus determined by a logistic regression analysis.

	Wald χ^2 score	OR (95% CI)	P
Non-obese			
Age	1.52	0.91 (0.91-1.02)	0.22
HbA1c at baseline	0.08	0.97 (0.77-1.19)	0.78
Therapeutic method	5.76	0.24 (0.07-0.74)	0.02
Obese			
Age	0.32	1.01 (0.97-1.06)	0.57
HbA1c at baseline	4.27	1.31 (1.02-1.71)	0.04
Therapeutic method	5.12	0.35 (0.14-0.87)	0.02

Adjusted by age, HbA1c at the baseline, and the therapeutic method (diet, oral hypoglycemic agents + insulin).

OR: odds ratio, CI: confidence interval.

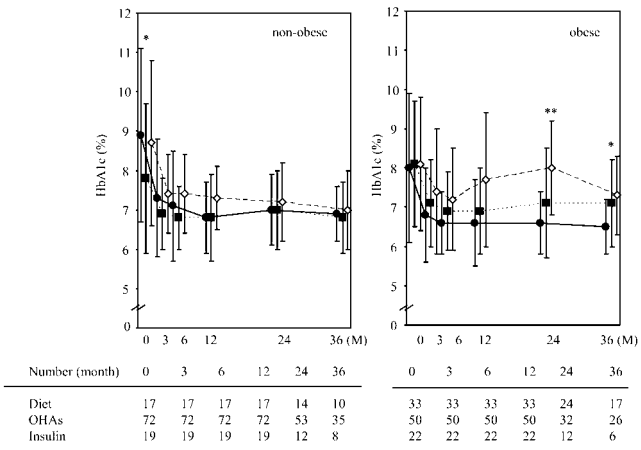

*Figure 4. Changes of HbA1c levels among the patient subgroups divided according to therapeutic methods prior to the initiation of metformin in the non-obese (left) and obese (right) patients with type 2 diabetes mellitus. Data represent the mean ± SD. Closed circles, closed squares and open squares represent the diet, oral hypoglycemic agents (OHAs) and insulin therapies, respectively. * P < 0.05 and ** P < 0.01 among three treatment groups.*

in the non-obese group (598 ± 132 mg/day at 12 months, 614 ± 138 mg/day at 24 months and 677 ± 184 mg/day at 36 months) than in the obese group (678 ± 169 mg/day at 12 months, 696 ± 170 mg/day at 24 months and 724 ± 117 mg/day at 36 months). However, the dose of metformin after body weight correction was significantly higher in the non-obese group than in the obese group over the course of the observation periods (Figure 3). The values of BMI were not significantly different through all periods in the two groups (Figure 2).

The correlations of the clinical parameters to the reduction of HbA1c are shown in Table 2. Only HbA1c levels at the baseline time were significantly correlated with the reduction in each time of the observation period, although the duration of diabetes mellitus only showed a correlation at 1 year after the initiation of metformin.

None of the patients were omitted from the study due to the side effects induced by metformin. Three patients discontinued metformin because of the progression of renal

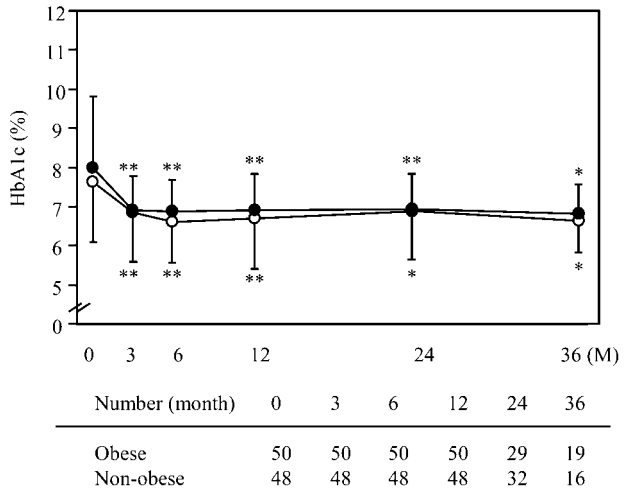

*Figure 5. Changes in HbA1c levels in patients who required no additional antidiabetic agents or a reduction in treatment. Data represent the mean ± SD. Open and closed circles represent the values in obese and non-obese individuals, respectively. * P < 0.05 and ** P < 0.01 vs. 0 M (initiation of metformin).*

dysfunction in both obese and non-obese groups during the observation period (Figure 1). After starting the metformin treatment, three patients (3%) in the non-obese group and 6 patients (6%) in the obese group were introduced onto insulin therapy. Additional OHAs besides metformin were required in 43 (40%) of the non-obese and 31 (30%) of the obese patients. Forty-eight (44%) and 50 (48%) patients required no additional antidiabetic agents (other OHAs or insulin) or a reduction of the treatment in the non-obese and obese groups, respectively. The other OHAs besides metformin were either reduced or discontinued in 10 (9%) of non-obese and 10 (10%) of obese patients. One (1%) of the non-obese and 5 (5%) of the obese patients no longer required insulin therapy. The proportion of the changes in these treatment components was not significantly different between the non-obese and obese groups based on a χ^2 test. Table 3 shows the odds ratio for the requirement of additional agents (other OHAs or insulin) in the non-obese and obese patients with type 2 diabetes mellitus according to a logistic regression analysis adjusted by age, HbA1c at baseline and the therapeutic method (diet = 0 and oral hypoglycemic agents plus insulin = 1). The treatment using additional agents was significantly more frequent in the individuals with diet therapy alone at baseline than in those using other glucose-lowering drugs in both non-obese and obese patients. The use of additional agents was also required more frequently in the patients showing high HbA1c levels at the baseline among the obese group. The model adjusted by the duration of diabetes mellitus, HbA1c at baseline and the therapeutic method showed similar statistical results (date are not shown).

Figure 4 shows the changes of HbA1c levels among the subgroups as divided by therapeutic methods (diet only, OHAs and insulin) at the baseline in the non-obese and obese patients with type 2 diabetes mellitus. Although HbA1c was significantly lower in the subgroup using OHAs at the baseline time, the changes in HbA1c levels during the observation period were not significantly different among the three subgroups in the non-obese patients. On the other hand, HbA1c was significantly higher in the subgroups using OHAs or insulin at 24 and 36 months in the obese patients.

To possibly minimize any interference caused by known changes in the other OHAs or insulin during the observation period, the changes in HbA1c levels were compared in the patients who required no additional antidiabetic agents or reduction in treatment between the non-obese (n = 48) and obese groups (n = 50). The course of HbA1c levels was not significantly different between the two groups (Figure 5). The reduction of HbA1c was 1.1% and 0.9% at 12 months, 1.1% and 0.8% at 24 months, 1.2% and 1.0% at 36 months in the non-obese and obese groups, respectively.

Discussion

This study demonstrated the long-term beneficial effect of metformin therapy in non-obese (BMI < 25 kg/m^2) patients with type 2 diabetes mellitus. Metformin induced a significant reduction in the HbA1c levels in non-obese patients. This effect was similar between non-obese and obese subjects who needed no additional antidiabetic agents or a reduction in other treatments during the observation period (Figure 5). Furthermore, similar glucose-lowering effects were obtained

among the non-obese subgroups divided by the therapeutic methods prior to the initiation of metformin (Figure 4).

Although several studies have shown the advantage of metformin in non-obese diabetic patients [6-12] , the observation periods were relatively short. Kaku et al. reported that the reduction of HbA1c by metformin was not different between 303 non-obese (0.9%, BMI < 25 kg/m^2) and 300 obese (1.0%, BMI ≥ 25 kg/m^2) Japanese patients with type 2 diabetes mellitus according to a prospective study for 12 months [6] . Hosokawa et al. retrospectively showed a significant 0.79% reduction in HbA1c levels in 58 patients with a BMI ≤ 22 kg/m^2, 0.81% in 81 patients with 22 < BMI < 25 kg/m^2, and 0.73% in 136 patients with 25 kg/m^2 ≤ BMI 12 months after the initiation of metformin for type 2 diabetes mellitus [7] . Clarke and Campbell reported that metformin monotherapy (n = 98) was equally effective as chlorpropamide (n = 91), one of the sulfonylurea agents, on blood glucose control without HbA1c measurements, and that metformin was superior in the body weight control in non-obese patients with type 2 diabetes mellitus according to a prospective study for 1 year [8] . Yajima et al. demonstrated the metformin administration at a dose of 500-750 mg/day to be more effective in non-obese patients (n = 22, mean BMI was 25.6 kg/m^2) with type 2 diabetes mellitus than in those treated at a dose of 150-300 mg/day of acarbose, an α-glucosidase inhibitors, in a crossover study conducted with 3-months treatment periods [9] . Lund et al. described that the glycemic regulation was equivalent between metformin and repaglinide, an insulin secretagogue, in a 4-month crossover trial in 96 non-obese (BMI ≤ 27 kg/m^2) European patients with type 2 diabetes mellitus [10] . They also reported that the effect of metformin (n = 52) and repaglinide (n = 49) was not significantly different when combined with insulin for the treatment of non-obese patients, according to a randomized prospective study for 12 months [11] . Donnelly et al. showed the glucose-lowering effect of metformin to be very similar between the non-obese and obese patients with type 2 diabetes mellitus according to a study covering a period ranging from 3-12 months [12] . Ong at al. revealed that metformin was efficacious in non-obese subjects with type 2 diabetes mellitus (n = 136) according to a retrospective analysis of 16 years [17] . This is the first report to show the long-term effect of metformin among obese and non-obese patients with type 2 diabetes mellitus. Although the definition of non-obese was a BMI of less than 30 kg/m^2, their investigation included 7% (n = 27) of individuals with a BMI < 25 kg/m^2 in their study subjects.

The glucose-lowering effect of metformin might be overestimated in the present study because the HbA1c levels were obtained from patients who had used metformin for more than one year. Individuals who stopped this treatment because of a lack of efficacy or side effects within one year were excluded. However, this limitation could be similar between the non-obese and obese groups.

The effects of OHAs and insulin gradually decrease as the treatment periods become longer [2,13] . Successive reduction of insulin from the pancreatic β-cells in patients with type 2 diabetes mellitus is considered to be a major factor for this attenuation of the drug effects [18-20] . The present study showed that a gradual increase of the metformin was required to control blood glucose levels during the observation period. However, the metformin dose increase was significantly lower in non-obese patients than in obese patients. Specifically, it may be possible to treat non-obese diabetic patients using a lower dose of metformin compared with obese patients. Donnelly et al. also reported that metformin was more effective in type 2 diabetic patients with a lower BMI [12] . However, the dose of metformin was higher in the non-obese patients than in the obese patients after the body weight correction in this study (Figure 3). It seems to be a paradox that a lower total dose of metformin while at the same time a higher dose corrected for body weight was found in the non-obese patients. In the present study, the duration of diabetes mellitus was significantly longer in the non-obese patients than in the obese patients. Furthermore, other glucose-lowering therapies, including OHAs and insulin were more frequently administered to the non-obese than to the obese patients. This underscored a potentially more severe stage of disease in the non-obese rather than in the obese patients. It is therefore possible that the endogenous insulin secretion was more strongly impaired in the non-obese than in the obese group, while the insulin resistance caused by, for example, visceral fat also was less in the non-obese than in the obese subjects of the present study. Although the parameters indicating insulin resistance and endogenous insulin secretion, such as serum or urine C-peptide concentration, were not evaluated in this study, the lower insulin resistance and secretion in the non-obese patients might have caused an increase in the requirement per body weight of metformin.

The levels of HbA1c were maintained within less than 7% during the 3-year observation period of this study. Additional OHAs or insulin treatment was necessary in 46 (43%) non-obese and 37 (35%) obese patients. It may also be caused by the attenuation of endogenous insulin secretion [18-20] . However, approximately half of patients required no addition or reduction of other treatments after the initiation of metformin in either group. Although the present study was not performed using metformin monotherapy, our results clinically demonstrated the advantage of metformin either in combination with the other antidiabetic agents or as a single therapy without any change in the treatment.

Metformin appears to maintain the glucose-lowering effect even after the observation period of this study had concluded, because the dose in the non-obese group was limited to 677 mg at 36 months of this study. The worsening in glycemic control over time observed in many patients with type 2 diabetes mellitus can probably be attenuated by increasing the dose of metformin because metformin reduces the HbA1c levels in a dose-related manner [21] . Metformin is a tolerable drug for patients if the dosage of the first year is completed, because no patients were omitted from this study due to side effects caused by metformin.

The results of this study have several limitations that must be considered. First, the findings are inherently limited by an inability to eliminate the effects caused by the other glucose-lowering agents, because our investigation included patients receiving a combination therapy of metformin and other antidiabetic drugs. It is difficult to study the long-term course of metformin monotherapy because of the attenuation of the effect as time passes [2,13] . Only 11 (3 non-obese and 8 obese) patients were treated with metformin monotherapy during the entire period, thus making it impossible to determine the significance of the therapy in these patients. To possibly minimize the interference caused by known changes in the other OHAs or insulin, the changes in HbA1c levels were compared in the patients who required no additional

antidiabetic agents or reduction in treatment between the non-obese and obese groups (Figure 5). Although the change in the insulin dose is considered to be important among the patients receiving insulin treatment at baseline, this factor was not investigated in the present study. We therefore cannot exclude the possibility that some differences in the need for increasing the insulin doses between the non-obese and obese group of patients confounded our data with respect to the efficacy of metformin treatment during this study. This factor could also be a confounder even in those patients with no known (other) changes in the treatment. Second, this investigation is a retrospective study without the obvious criteria for the changes in treatment methods. Because the optimization of the metformin dose and the coordination of the treatment were dependent on each patient's physician, we considered that errors on the effects of metformin could have occurred. Third, the present study did not include a control group with a different treatment regimen, such as insulin secretagogues. Therefore, it is unknown whether the observed similarities and differences between the non-obese and obese patients were specific for these groups and/or specific effects of metformin therapy. Fourth, the associations of metformin with diabetic vascular events were not examined in this study. Furthermore, the risk factors for cardiovascular diseases such as blood pressure and serum lipid profile were not analyzed during the observation period because various antihypertensive agents and statins were used. The results of this study demonstrated the glucose-lowering effect of metformin in a group of non-obese patients with type 2 diabetes mellitus who continued such treatment for at least 1 year. Therefore, investigations to evaluate the effect of metformin therapy to potentially reduce the risk of developing diabetic complications also in non-obese patients with type 2 diabetes mellitus should be considered in the future.

Declaration of competing interests

The authors declare that they have no competing interests.

Authors' contributions

HIt and HIs contributed to the design of the study, analysis and interpretation of data, and drafting of the manuscript. YT, SA, MA, MM and MT contributed to interpretation of the data and critical revision of the manuscript. All authors have given their final approval of the submitted version of the manuscript.

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Cognitive cibernetics

Vladimir Ivanov, Alexandra Ivanova (Khayrulova)

The great physiologist Ivan Pavlov once said "The human being is a self-adaptive, self-improving and self-developing system". Lots of research has been devoted to this phenomenon, but why? And what is the end goal that this research works to helps us reach? In our attempt to understand human psychological activity, the key to the mystery can be found within the works of the internationally recognized Russian physiologist P. Anokhin.

"Moreover we must not forget that all the richest research about conditioned reflexes and general physiology are reasonable only if they at least marginally draw us to the comprehension of driving forces and the nature of human behaviour and psychic activity" (Anokhin, 1969).

Each person born on Earth at least once in his life has thought about his particular feelings and tried to make his life better on account of them: a chronically ill person trying to heal himself, a drug addict trying to break his addiction, a coward trying to become braver. Feeling is the keystone of all human reasoning. Since every one of us knows that any kind of behaviour varies and is performed at the behest of our emotions.

Let's consider this: We know that reality is reflected in us through the higher nervous activity as stated by the Nobel Prize winner Ivan Pavlov. Behaviour performance therefore generates functional systems which perpetuate according to the learning principle. If the functional system is a theoretical multiuse principle, does it mean that such systems can be formed with the participation of the thinking activity of a person? If so, what do the components of these cognitive systems look like? How do the functional systems' signs manifest themselves in thinking?

Conditioned reactions may differ by their latency period length, by the speed of differentiation output or by the track of the extinction curve and nothing more. Their difference in biological quality and their fundamentally different biological significance for the shaping of active behaviour is not taken into consideration. This biological significance is also attached to those reactions caused by emotions. It is emotion which gives an aspect to an effector expression of a conditioned reaction by joining in any reaction. The formation of behaviour is always linked to the emotion generated by a situation. Our reaction to situations is something different and greater than merely some secretion, rapidity of action and other physiological characteristics. Yes indeed, how the emotions of different people are acting out is more or less visible, but the negative effect that these emotions bring to internal organs' processes does not thereby decrease.

"Emotion is a complex of processes, by which its morphogenetical origin and physiological qualities is unfolding like an integral functional system according to a consistent pattern, relying cortex and diencephalic apparatus. …It represents precisely harmonized courses of central and humoral processes. This harmonization is so peculiar in every specific case that it does not allow different emotional expressions to mix biologically together such as laughter, tears, anger, joy etc". (Anokhin, 1974)

Vladimir A. Ivanov

Private psychological practitioner, member of expert council of the security Committee of the State Duma (lower chamber of Russian Parliament), member of the advisory board of experts of the State Anti-Drug Committee of the Central District of the Russian Federation. He developed the following technologies of emotions' treatment: "Iterative extinction" and "Sense of calmness" in Moscow in 1997.

Alexandra V. Khayrulova (Ivanova)

Private psychological practitioner. Winner of "Psychologist of the Year European Award 2010". Together with V. Ivanov she has been adopting Vladimir's methods in different fields for 11 years. She has experience in treatment of drug and alcohol addiction, depressions, phobic and nervous disorders, panic attacks, bulimia and anorexia, I and II types of diabetes, bronchial asthma, eczema, disseminated sclerosis, hypertension and more than 20 other diseases. Preflight pilot training, athletes pre-event preparation are also part of her professional experience. Famous Russian coaches, athletes, businessmen and officials were among her patients.

The physiological side of emotion has been experimentally justified but how is it related to human psychology, behaviour and health? This is the key question the answer to which will yield an understanding of the emotions' nature. It will also help in the creation of technologies of human psychic and physical health maintenance and for behaviour control.

So if emotion is a functional system with all its qualities, that means it has its adaptive result, action acceptor, afferentation and feedback. We as psychologists are interested in what it is. How is the functional system represented in human thinking? Every one of us thinks and all of us know that thinking consists of a cycle of intellectual operations with images of subjects, images of actions and images of feelings. Consequently, these intellectual operations must form and constitute a functional system in thinking, viz. emotion. Intellectual actions are the cognitive components of the system.

Let's look back at what physiologists consider as an action result acceptor. These are parameters of a useful result: the goal of behaviour. How are the parameters of a useful result represented in thinking? This is an image which contains a model of the future or in other words our expectations. Afferentation is also carried out by intellectual operations: highlighting a figure against the background, denomination, classification, synthesis, analysis, assigning significance etc. Additionally, feedback is an intellectual act of comparison of the obtained image of reality with the expectations.

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This description of emotion's cognitive structure doesn't contradict and on the contrary is absolutely in line with the theory of functional system and functions according to the principles that Anoknin discovered.

A long time ago, Russian physiologists introduced a notion of "forced function of a system's component" for a clearer understanding of emotions. We'll also use this term to understand when exactly the formed emotion, being a central integration, forces thinking to participate in a reaction, in the process of emotional experience.

Within the hand's large muscle complexes, while the hand is making a targeted movement, many muscles constrict according to the forcing principle. It is this rule that makes many diseases "incurable". A disease, once it has emerged according to the learning principle, will steadily reproduce itself exactly in the situations which prompt the emotion that originally provoked that kind of behaviour. How many cognitive components are necessary for an emotion to appear? A limited number of triggering afferentations of the human mind (just several ideas or images) is enough for drug addiction or diabetes to develop, and almost none of the peripheral regulating impulses are needed. Many animal experiences have proved this since the 1970's. With the lapse of time and through training, this forced participation of an organism in feelings expands the forced components' composition, becomes automated and contracts the afferent structure of the system. One idea, word or image is enough to trigger the development of the entire system. It will continue until the emotion that created the system stops being centrally integrated.

Physiologists say that all effector components, especially the internal ones, viz. cardiovascular, intestinal and other, almost always accomplish the emotional effect, even if their motor components are not identified at all. Even if a mimic expression is suppressed, all other components for example: vasomotor ones (blush), may be entirely expressed. The images composing the emotion's cognitive components will remain in conscience. All visceral pathologies and psychic addiction are clear thereupon and this is the point of psychological treatment! If a person gives up drugs by willpower, he still yearns for them. "We cannot remove an emotion, we can only switch its expression from one effector apparatus to another one", Anokhin believed, "… because humans do not dispose any mechanism of the emotion's reverse regulation from the visceral organs". If our face expresses an offence or fear, it does not mean at all that we feel the corresponding emotions.

Nevertheless today, thanks to professor Yury M. Orlov and his theory of sanogenic thinking we can do more. Developing his ideas today, we can stop the emotion's unfolding by changing the type of the central integration not by willpower but by changing or stopping afferentations and their composition. Each morale has corresponding ideas and images. Images of calmness and thoughts about it differ from images of offence and thoughts about it and a human person feels their biological difference by the way how tensions are distributed all over the body, and we can feel this distribution. If a person manages to keep himself in state of calmness while he is thinking about an offence, the destruction of the offence is inevitable, extinction of the related reactions, including internal ones, is unavoidable. This is the main conclusion Orlov has made using the abovementioned approach.

As a longterm interference of emotion and redirection of all its power of expression inside the human person provokes a lasting pathogenic functioning of visceral organs, extinction is the key problem for a doctor. To destroy a functional system, the volume of afferentation -the relavant ideas and images- must be smaller than that one which is sufficient for the maintenance of the system and for bringing it to an adaptive effect. A system's destruction is not possible before its adaptive effect is removed. The system destructs at the very moment the minimal afferentation limit for the system is overcome.

One might ask what drug addiction looks like from this point of view. Drug addiction is a recurrent drug making and taking, it's a central integration of nervous, humoral and cognitive processes where cognitive components are represented by a succession of intellectual actions operating images of making and taking narcotics including image of "getting high". Before it is experienced for the first time, the cogitation draws up a succession of images of objects and actions which will constitute the drug making image and the desired result anticipation. When euphoria is achieved it sustains and returns and little by little it becomes the most dominant of the notions of the conditional reflex. A morbid addiction is exactly this kind of image succession. Thus, if it is possible to "see" the addiction, it is therefore possible to identify this succession of images. These images turn out to be not only cognitive components of the system, but they start playing the role of exciters which trigger the conditioned reaction. It's enough for a drug addict just to have a look at a drug pack for thinking to start participating in the addiction development through preparations that trigger narcotic behaviour. Such is the forced function of thinking in the cognitive system of drug addiction.

We have achieved the creation of a diagnosis form for checking out a pathological narcotics addiction. We have been successfully using it for more than 10 years. Thanks to it we can define whether a patient is a drug addict or not and identify the number of excitors and the afferent composition of the cognitive system components. In this regard we should say that in drug addiction treatment, it is possible to overcome the afferent minimum if we completely remove all the ideas about narcotics.

As any functional system exists on condition that it has a useful result, we should say some words about the estimation of the result value. Estimation of the system's result value is a higher order principle and it identifies the place of the system in the life of the entire organism. That means we should understand what the drug addiction's useful result is which is the easing of distressing emotions. The use of narcotics eases pain, offence, fear, loneliness and other painful distressing emotions. These processes, after having been practiced, include temporary connections' elements that Pavlov discovered. That's why we can consider narcotics addiction as a functional system and consequently, it is possible to treat it by extinction of afferent minimum. That was done by psychologist Vladimir Ivanov in 1997 in Moscow.

How does one extinguish an emotion's effect? Emotion does not emerge if the central integration does not receive

any reverse excitement from the acting organs. In other words, if we calm a component of the system, we will get the extinction by repeating successfully in the mind all the operations with narcotics. And it is only thinking which can help us to remain calm, because it is thinking which makes an estimation of the cognitive result's value.

The abovementioned reasoning has led to the development of five cognitive technologies. Each of them represents an instruction or an algorithm of thinking which aims at the destruction of emotion or another functional system containing cognitive components. Those are a sense of calmness, three kinds of iterative extinction and the system of states modeling.

When scientific research develops this idea and finally considers human emotions as functional systems with their components consisting of ideas and images, the psychologists will then have at their disposal an outstandingly powerful instrument for the psychological treatment of patients.

On condition of providing specialized pharmaceutical care for professional workers and patients with occupational diseases

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In modern social and economic conditions working out and realization of the new concept of the care is necessary for the able-bodied population uniting a medical and pharmaceutical component. In this connection actual there is an all-round studying and working out of organizational-methodical base of the specialized pharmaceutical help for working in harmful and dangerous conditions of production, and also patients of occupational diseases. For this purpose it was necessary to carry out the essence and concept pharmaceutical care analysis, including specialized, to reveal the basic directions of the pharmaceutical care and forms of its rendering.

Last two decades in world pharmaceutical practice transition from medicinal maintenance to wider professional work – the pharmaceutical help is obvious. According to definition of World Health Organization and the International pharmaceutical federation, pharmaceutical care is connected with responsible granting of pharmacotherapy for the purpose of achievement of the certain results improving quality of life of patients [14]. Pharmaceutical care represents system of maintenance of the medicinal therapy, providing the complex of actions including consultation, scheduling of medicinal therapy, supervision over the patient during treatment, an estimation of results of treatment of the patient etc. Pharmaceutical care differs from traditional pharmacy the orientation to social requirements [26].

Purpose of the pharmaceutical care is improvement of quality of life of consumers of medical products by achievement of the guaranteed clinical results at optimum economic expenses. System of the pharmaceutical care is directed on the prevention and-or the decision of already existing problems of the patient connected with reception medicines. Pharmacists become obligatory participants of medical process with a view of maintenance of optimum therapeutic results. In sphere of their professional competence is not only selection, wholesale purchases, storage, distribution,

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holiday ЛС, recommendations about correct reception medicines but also as granting of services of the highest quality services in the concept of "the pharmacist of 7 stars», ability to make well-founded decisions, management and communicative skills, readiness for leadership, ability to learn others and most to study, inclinations of the researcher and desire to use scientific knowledge in the practical purposes. It assumes formation of new type of mutual relations between the pharmacist, the patient and the attending physician, namely participation in a substantiation of choice medicines, consultation and training of the patient to rules of reception medicines, monitoring of medicinal therapy, an estimation of results of medicinal therapy database conducting about the patient and medicines, given to it [27].

As object of the pharmaceutical help the individual and a society (group, population of patients) can act.

The individual pharmaceutical help is directed on scheduling of medicinal therapy, achievement of success of pharmacotherapy, preventive maintenance of by-effects from drug intake, tracing of a course of treatment, its updating [17].

The pharmaceutical help or the service turned to a society, is directed on formation of the medicines lists, official directories, the analysis of results of researches in sphere of consumption of medicines and their cost, working out of elements of a national policy in sphere of medicinal maintenance.

In many countries the wide experience on rendering of the pharmaceutical help including at separate conditions and diseases, such as the diabetes, a hypertensia, an asthma,

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гиперлипидемия, chronic pains, rheumatic illnesses, mental frustration, etc. Thus appears individual pharmaceutical which consists in support of the patient on all questions of pharmacotherapy, a state of his health, participation in training programs [13, 16, 29] is saved up. There were new professional services with participation of the pharmacist: participation in vaccination, in house hospitals [23, 25]. The problem of rendering of the specialized pharmaceutical help for various age categories of the population especially for children and elderly persons [18, 27] is actual.

Data of poll spent among pharmacists of Switzerland and Germany, about essence pharmaceutical care has shown that pharmaceutical care consists in medicinal maintenance, maintenance of individual pharmacotherapy, information-consulting services and quality assurance of work [15]. The information services rendered to separate patients and the pharmaceutical companies, are considered as a part of strategy of a survival of a trade and economic component pharmaceutical care [20]. Many foreign authors consider the pharmaceutical care as a component of national system of public health services which is realized on local, regional, and national level and raises efficiency of all system of public health services [21, 24].

In the Russian pharmaceutical science the concept of the pharmaceutical help, including specialized, was formed for many years. Professor P.V.Lopatin offered definition of the pharmaceutical care as population maintenance with all goods of chemist's assortment, rendering of the scientific and advisory help to medical staff and separate citizens concerning a choice of the most effective medicines and other subjects of chemist's assortment, ways of their storage, use, an order of acquisition and etc [6].

L.V.Moshkova and coauthors consider that the pharmaceutical care is a complex of the actions directed on satisfaction of requirements of the population in acquisition of necessary medicines, products of medical appointment and other goods for maintenance and recovery of health. As criteria of efficiency of the pharmaceutical care the quantity of refusals, a waiting time, complaints have been offered, to gratitude etc. [7]. The problem of availability and demand for the pharmaceutical help, formed under the influence of structure and level of disease, demographic structure of families, cost of services, the family budget has been investigated by A.V.Fominoy [12].

In the Russian researches the direction clinical or specialized pharmaceutical care was generated. Concept of pharmaceutical care from the point of view of strategic management and as sets of pharmaceutical services has been formulated by L.N.Geller. It has allocated unspecialized, pharmaceutical care rendered by experts with pharmaceutical formation which includes popular, hospital, social both sanatorium pharmaceutical care, and specialized pharmaceutical care, rendered by the pharmacists who has received profound preparation. To specialized pharmaceutical care have been carried homeopathic, pediatric, geriatric, phytotherapeutic and clinical (with an asthma, a diabetes, a mammary gland cancer etc.) [3].

The great attention is deserved by L.M.Manojlovoj's work in which works it is possible to allocate separate elements of the specialized pharmaceutical care in the field of professional health of workers of drugstores: a control system of professional health, methodology of an administrative estimation of professional health and system of preventive maintenance with use of modern improving technologies [8].

The problem of the pharmaceutical care in A.I.Ovod's articles with coauthors is most full considered. Have been allocated object of the pharmaceutical help – the patient with concrete disease, a subject of the pharmaceutical care - quality of pharmacotherapy, main principles - an individual approach, interaction with the patient and the doctor during pharmacotherapy, regular increase of knowledge pharmacists in the field of pharmacotherapy of the given disease, the information on the medicinal help, psychology of dialogue, development of the market of medicines, observance of professional etiquette and confidentiality, standardization and control.

The purpose specialized pharmaceutical care is maintenance of appropriate quality of pharmacotherapy of the concrete patient with concrete disease, and problems - granting medicines of demanded quality, training of the patient to correct application of medicines, control of application of the medicines which have been released without the recipe, database conducting about the patient, the medicines released to it, cooperation with the doctor, informing of the doctor on medicines, a current and pharmacotherapy complications.

Result pharmaceutical care estimated documentary, represents improvement of quality of life of the patient.

Authors have offered complex definition of the pharmaceutical care as systems of medicinal, information and organizational-methodical maintenance of the individualized pharmacotherapy of concrete diseases [10, 11].

For representation formation about the specialized pharmaceutical care for the worker of the population and sick occupational diseases by us had been revealed features and tendencies in professional disease.

Now all over the world the tendency to growth of professional disease is marked. The World Health Organization allocates the reasons of positive dynamics in professional disease: the weak legislation of some the countries, occurrence of new dangerous technologies and production, migration of labor, growth of informal economy, discrimination on a workplace, social distinctions of the population.

Russia occupies 24 place on professional disease in Europe [2]. Real level of professional disease in Russia in tens times above nowadays registered. One of the reasons of such situation is that in Russia professional is considered chronic or the acute disease which resulting influence of harmful production factor and has entailed time or proof loss of professional work capacity while the international organization of work professional considers the disease which has developed as a result of influence of risk factors, connected with labor activity [22]. As a result of these distinctions in definition of occupational diseases in the Russian Federation many diseases formed as a result of professional work, don't concern the professional.

Thus in the country there are conditions which promote low actual level of professional disease: imperfection of the legislation on a labor safety, absence of legal and economic sanctions for concealment occupational diseases and

poisonings, lacks of the organization and carrying out of preventive medical inspections working [1, 4].

Occupational diseases have the huge mediko-social importance because directly define labor potential of the country, and also affect a condition of reproductive health [5]. The medicinal help which rendering is declared by the standard documents accepted concerning health of workers and sick occupational diseases becomes the Integral part of mediko-social security of the working population and sick of occupational diseases.

So, in the Federal Law-125 «About obligatory social insurance medicinal maintenance is guaranteed against accidents on manufacture and occupational diseases» at: treatment insured, carried out in territory of the Russian Federation directly after the occurred heavy accident on manufacture before restoration of work capacity or an establishment of proof loss of professional work capacity; acquisition of medicines, products of medical appointment and individual leaving; medical rehabilitation in the organizations rendering sanatorium services, including in the permit, including payment of treatment, residing and a food insured.

To the patient with the diagnosis of occupational disease or with suspicion on it there are following kinds of medical aid: out-patient-polyclinic professional pathologies rendered in the center, polyclinic in a residence, a medico-sanitary part; stationary professional pathologies rendered in the center, a medico-sanitary part and other establishments; sanatorium rehabilitations rendered in the center. The medicinal help to the working population, to patients and invalids with professional diseases takes place at all stages of rendering of medical aid, and the state guarantees preferential medicinal maintenance in case of industrial traumas, accidents and physical inability on occupational disease.

The analysis of rendering of the professional pathological help and standard documents in the field of medicine of work and a professional pathology shows absence, and also necessity and possibility of the organization and working out of methodical maintenance of the specialized pharmaceutical care. On the basis of the spent analysis of concept and the maintenance of the pharmaceutical care, features of professional disease, health services of workers and sick occupational diseases, us it is defined specialized pharmaceutical care in the field of occupational diseases as system of medicinal, information and organizational-methodical maintenance of farmako-preventive maintenance, therapy and the rehabilitation of occupational diseases realized in hospital, out-patient sectors of public health services, the general pharmaceutical practice at various levels (local, regional, national) and rendered by experts with the pharmaceutical formation, received profound preparation.

For rendering of the qualitative pharmaceutical care in the field of a professional pathology we had been developed the base methodical complex consisting of standard and methodical materials the part from which has received practical introduction. Into the base complete set of documents have entered organizational-functional model of the pharmaceutical care at occupational diseases; the standard of the pharmaceutical care at occupational diseases; position about chemist's point of the industrial enterprise, the program of the pharmaceutical care for workers at the large industrial enterprises, realized in the chemist's organization serving the population; algorithm of service of patients at occupational diseases; the program of preparation of experts with profound preparation on the pharmaceutical care in the field of occupational diseases; methodical recommendations about working out of official lists, organizations pharmaceutical care at occupational diseases.

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Giant form of mandibular hypercondyle: surgical treatment

G.E.Khachatryan

Surgical treatment of pathology of temporomandibular joint (TMJ) is one of the important parts of orthognathic surgery of the jaws. Accordingly, one of the reasons of disgnaty of the jaw is hypertrophy of articular processes of the mandible, which leads to hypercondyle and secondary deformation of facial skeleton.

The information on this subject in native and foreign literature is not very rich. In this connection, we are faced with the need to clarify, streamline the diagnosis and choice of surgical treatment of deformations of mandible's articular processes.

In the past five years in the department of maxillofacial surgery of Clinical Hospital N3 in Yerevan were observed and operated approximately 23 patients with various pathologys of mandible's condylar processes.

The critical issue is the definition of diagnosis of the etiological factor of dento-maxillofacial region's deformation. The question is if the hypercondyle is the reason of maxillofacial region's deformation or it arises compensatory.

According to some authors and our own observations, the cause of the true or primary hypercondyle may be trauma. It is known that macro-trauma may lead to the defeat of germ band of condylar ridge, microtrauma can lead to the hypertrophy and it's hyperplasia.

For the differential diagnosis of hyperkondyle it is necessary to carry out X-rays of jaws, Magnetic Resonance Imaging (MRI), TMJ 3D-CT, teleradiography, panoramic X-ray, pneumoarthrography, craniometric study.

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Depending on the state of occlusion, we suggest to distinguish three types of unilateral hypercondyle:

1. The bite is not broken, occlusal plane is shifted, there is complete closure of dentition and complete the cutting-papulose contact (compensated hyperkondyle);
2. There is an open bite on the side homolateral to articular process (vertical hyperkondyle);
3. There is a cross-bite, the central interincisivial line has been moved to the healthy side (lateral hyperkondyle).

Depending on the form and severity of the disease we have different clinical manifestations and various degrees of deformation of dento-maxillofacial region.

During the planning of surgery, is set the main goal, which is eliminate the asymmetry and malocclusion.

The choice of methods of surgical correction depends on:

1. On the extent of secondary deformities of maxillofacial

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region (strain angle and the chin of the lower jaw);
2. The extent of deformation of the upper jaw and the extent of secondary damage of the healthy joint.
Fundamentally operative treatment can be divided into two types - a monooperation (condilektomy) and combined operations (condylectomy combined with osteotomy of the upper and lower jaws (osteotomy by Dal Ponte, genioplastic surgery, correcting osteotomy of the maxilla, resection of the hypertrophied fragment, transposition of n. alveolaris inferior etc.).
According to our observations, in 70% of cases there is a need of multilevel operations in conjunction with condylectomy. In 30% of cases, they were both monooperation (condilectomy), which led to complete recovery, and the correction of secondary deformities malocclusion conservative manner (orthodontic treatment, miogymnastic).
The most appropriate prompt access during operations on the articular process of the mandible, from our point of view is temporal access, which is based on the literature, most often used in international practice of surgical treatment of diseases of the TMJ. Aesthetically, this access is the best, as the cutting line, as well as postoperative scar remains in the area of hair. From a technical standpoint, it is more convenient, less traumatic and allows to have a wide operative field.

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Novel "niche-relief" conception for human stromal stem cells and its application to osteogenesis imperfecta diagnostics

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At present, a few proposals about opportunity of existence of hypothetic "niche" for multipotent mesenchymal stromal cell (MMSC) and its descendants are presented. Aim of current research is connected with experimental investigation of some parameters of artificial microterritories facilitating osteogenic differentiation of stromal stem cells. Technique of short-term culture of human lung prenatal stromal cells with fibroblast-like morphology on calcium phosphate (CP) substrates with known topography was used. According to cell culture (osteocalcin, alkaline phosphatase (ALP)) secretory activity, MMSC interacting with CP discs directly obtain advantage in display of osteoblast-like functional activity in comparison with cells on plastic surface. Implants with "smooth" CP coatings (Ra<1 μm) are less suitable for bone tissue regeneration in consequence of high expectancy of TNFα cell secretion promoting to "quiescent" niche state. CP rough surfaces (Ra>2 μm) stimulate formation of three-dimensional culture of human MMSC. Cells staining positively for acid phosphatase are located on spheroliths forming relief of CP coating surface. ALP staining cells (osteoblasts' marker) populate sockets ("niches") of artificial surface. At that, "niche" for induction of human MMSC osteogenic differentiation is, apparently, a structural-functional concept. For its characteristics, it's appropriate to apply index expressing ratio of area of ALP staining cell to CP surface area occupied with stained cell (in vitro mean value of 43 % approximately). Niche index less than 32 % (smooth CP surface) is accompanied by in vitro suppression of human MMSC osteogenic differentiation

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and an inhibition of ectopic osteogenesis and hemopoiesis remodeling in mice.
Up to 18-29 % of stromal cells including clonogenic ones induced to in vitro fibroblastoid transformation by relief CP coatings can circulate within blood mononuclear leukocytes (BML) fraction of healthy donors. The methodology developed may be useful in application for diagnostics, cell therapy and tissue engineering. In particular, morphofunctional parameters of BML contacting in vitro with model implants are the probable markers and predictors of osteogenesis imperfecta course and duration of such patients' rehabilitation. At that, RANTES gene expression on human BML may be effective for methods of prediction of cellular inflammatory (osteolytic) answer, whereas CCR5 gene expression - in development of technique to predict bone tissue remodeling in reply to using different implants for osteosynthesis.

Grundlagen der Sporttherapie in Prävention und Rehabilitationen strukturelle Elemente und Methoden sporttherapeutischer Interventionen

Peter Klug

Die Sporttherapie hat sich als Variante der Bewegungstherapie- insbesondere im Bereich der Prävention und der medizinischen Rehabilitation- etabliert. Sporttherapeutische Interventionen auf der Grundlage fundierter medizinischer,- pädagogischer und sportwissenschaftlicher Kenntnisse werden angesichts der verstärkten Forderung nach Qualitätssicherung in diesen Bereichen immer wichtiger. Fragestellung: Erstens: Gelingt es durch eine wissenschaftlich fundierte und praxisrelevant aufgebaute Prävention eine verbesserte Gesundheitssituation herzustellen und dauerhaft zu sichern um so auch die Entstehung von Krankheiten weitest gehend zu vermeiden. Zweitens: Wie ist die Sporttherapie in der Lage beim Auftreten von Krankheiten und Schadensbildern durch ihren Methoden und strukturellen Elementen in Synthese mit Den anderen Therapieformen erfolgreich zu wirken. Methodik:

Sportwissenschaftler Peter Klug

• Wissenschaftlich fundiertes Studium der Sportwissenschaften
• Medizinisch orientierte Ausbildung zum Sporttherapeuten: • Orthopädie – Rheumatologie - Traumatologie –
• Innere Medizin
• Neurologie
• Psychiatrie und Suchtmedizin Medizinisch, -sportwissenschaftlich und -pädagogisch determinierte Konzepte zum Aufbau einer lang anhaltenden Gesundheitskompetenz beim Patienten. Ergebnisse: Zeigen sich in diversen Studien und Untersuchungen und bei der Auswertung von Therapieergebnissen.

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Der Einfluss von Sport Und körperlicher Bewegung auf Adipositas, biochemische und physiologische Wirkmechanismen, Realistische Therapieansätze

Peter Klug

Fragestellung:

In welchem Maße ist eine sinnvolle Kombinationstherapie von gesunder Reduktionskost und belastungsadäquater Bewegung, erfolgsversprechend auf dem Weg zur Reduktion des Körperfettanteils, bei gleichzeitiger Erhaltung oder sogar Zunahme der Körpermuskelmasse?

Methodik:

Leistungsdiagnostik im kardiopulmonalen (einschließlich Ergospirometrie) und motorischen Bereich.
Training aller Hauptmuskelgruppen in einem ausgewogenen Muskeltraining. Bei durchschnittlich 2 Serien a 20 Wiederholungen zu Beginn des Trainings und Ausdauertraining in der durch den Respiratorischen Quotienten festgestellten Fettverbrennungsbereich.

Ergebnisse:

Auswertung der Ergebnisse durch exakte Messung des Körperfettanteils mittels Fat-Caliper. Messung von signifikanten Teil-Körperumfängen zur Ermittlung des Fettverteilungsmusters. WHO-Stufentest auf dem Fahrradergometer zur Feststellung der Kardiopulmonalen-Leistungsfähigkeit.

Opportunities of unconventional medicine at correction of infringements of intersystem interactions in an organism of the person

Leonid Kosmodemjansky[1], Timur Bashir-Zade[2]

In 1993 the British medical association has suggested to attribute the various methods which have been not connected to orthodox medicine, to the methods of unconventional therapy. Such methods concern to them as acupuncture, homeopathy, herbal medicine, kinesiology, etc. which distinctive feature is that their action it is directed, mainly on an organism of the person in the whole as uniform automatically adjusting system, making active protective forces of an organism, resulting to normalization of intersystem infringements. In a basis of the medical effects these methods have restoration of such parameters homeostasis as "energy" and "information" which today appeared outside of sphere of attention of methods of orthodox medicine.

The basic purpose of the carried out researches was the estimation of efficiency of some methods unconventional therapy: magnetic-pulse; colour-dynamic therapies; bioresonance therapy; acousto-K-laser therapies and the homeopathy, the infringements of intersystem interactions directed on correction in an organism of the person on mental , psychophysiological and physiological levels of functional systems . The choice of methods and technologies of rehabilitation was spent on the basis of an estimation of a level, character and a degree of expressiveness of the intersystem infringements estimated with the help

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probabilistic of function entropy considered under formula Shannon, and also the analysis of adequacy, features of application and opportunities of ways and means of restoration . The similar approach, in our opinion, should provide restoration of the broken intersystem interrelations and, as consequence - a due level of health, since allows precisely enough help the doctor concerning necessity, efficiency, a kind, intensity and so forth characteristics correct influences.

Results of the the carried out researches have allowed to reveal specificity of separate and complex rehabilitation technologies concerning a kind and character of infringements :

- the most effective methods of correction of infringements at level intersystem interactions and psychophysiological functions were magnetic-pulse and colour-dynamic therapy, and also complex influence magnetic-pulse + homeopathy

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+ colour-dynamic therapy; the observable increase entropy has made - 42 %, 37 % and 48 % accordingly;
- the most effective methods of correction of infringements at level intersystem interactions psychophysiological and physiological functions were magnetic-pulse and homeopathy, and also complex influence magnetic-pulse + homeopathy + acousto-K-laser; the observable increase entropy has made - 52 %, 45 % and 58 % accordingly;
- the most effective methods of correction of infringements intersystem interactions psychophysiological and physiological functions were magnetic-pulse and bioresonant therapy , and also complex influence magnetic-pulse + homeopathy + bioresonance therapy ; the observable increase entropy has made - 58 %, 56 % and 67 % accordingly.

The steadiest both mono, and complex therapy were infringements at level psychological and psychophysiological intersystem interactions , least -psychophysiological and physiological functions. These data, apparently, testify to the certain sequence of formation of intersystem infringements in an organism, those under influence those or other factors of environment: primarily infringements are shown at level psychophysiological and physiological , then at level physiological-physiological and further at level physiological-psychophysiological. Restoration of functions at carrying out of therapy is observed in the same sequence.

The carried out investigations have allowed to draw a conclusion that the most perspective concerning correction of infringements of intersystem interactions in an organism are the methods of unconventional therapy possessing an opportunity of polysystem influence on an organism, carried out on physical channels of regulation. In particular magnetic-pulse and colour-dynamic therapies in which structure of programs the set organospecific frequencies is initially incorporated, allowing to realize in practice the given opportunity.

Application of modern technologies for correction of human body system interactions

Leonid Kosmodemjansky

S.Hanhemann in «Organon of medicine», more 200 years ago, has formulated main principles of the system analysis in estimations of infringements of a state of health of the person. Modern conception theories of functional systems, information biology and medicine, cybernetics and the mathematical analysis allow on new to look at homeopathy, as on modern technology of correction of intersystem interactions in an organism of the person. It is modern methodology of the analysis and an estimation of intersystem interactions in an organism of the person allows to make purpose of homeopathic preparation mathematically authentic and most probable reflection of all set of infringements of systems of adaptation.

For maintenance of the most full correct influences of a homeopathic medical product, in each concrete case, the individual approach in search and a choice of a required homeopathic preparation is required. In our opinion most effectively allows to solve this problem application of modern computer analytical systems on processings databases . With this purpose, within the framework of spent research on efficiency correct therapies of intersystem interactions with application of homeopathy, we had been developed and introduced the new software - «Diagnostic analytical repertorium» (DAR) (The certificate No 201061735) which meets modern requirements showed to expert systems. It is developed in view of basic principles of a homeopathic method of treatment and modern opportunities of computer programming, providing fast and reliable searches on the generated processings databases , allows carries out the all-round analysis of a case. Application new software essentially facilitates to formalize and optimize application of homeopathy as modern technology of correction of intersystem interactions in an organism of the person.

Chemiluminescence study of the influence of ozonization on the antioxidant activity of blood plasma in patients with urogenital infection

Yury I. Kozin[1], T.S. Dyubko[2,3], O.A. Sokolyk[2], A.D. Roshal[3,4], K. Krzymiński[5]

The recent decade has witnessed a major problem of wide spreading of the urogenital infections (UGI), which occur in 50-70% of sexual partners. In 30-35% of cases these infectious diseases cause by a polyvalent flora, combinations of trichomonads with chlamydiae, mycoplasms, viruses and candidal infection. In 40-45% of cases the urogenital infections become chronic, which is due to the development of the decompensated antioxidant stress and the secondary immune deficit of the injured organ. Taking into account that an overwhelming majority of chemical and organic immune correctors have not been standardized yet, the authors have been successfully applying ozone therapy as a method of physical-chemical correction for over 15 years. The above method enabled the authors to cure chronic urogenital infection of 876 (89.3 %) patients. Experimental clinical research, conducted by the authors, corroborated the immune-correcting influence of ozone therapy on all the major (cellular, humoral, mononuclear-phagocytic, interferon) links of the immunity. Considering the fact that antioxidant stress is the first link, testifying to the development of the secondary immune deficit, a study of the dynamics of blood plasma general antioxidant activity (AOA) of the given category of patients has become the barest necessity.

Antioxidant activity of blood may be corrected by different ways. Medicamentous and vegetable preparations are routinely used as bioantioxidants (antioxidant preparations), however, certain therapeutic physical factors also possess antioxidant activity. These factors include, e.g., low-intensity electromagnetic emission of the millimeter range with extremely high frequencies (EHF), utilized in a method of the EHF-therapy [1], and application of the ozone therapy methods, which stimulate host defenses and antioxidant defense as well. It should be noted that they are free of such defects as individual intolerance, which is typical for some medical products and drugs.

Intravenous injection of extracorporal ozone-saturated autoblood of patients into the blood bed is one of the means of modifying the antioxidant status [2, 3, 4]. Periodic monitoring of the dynamics of the blood antioxidant status is required for increasing the efficiency of ozone therapy treatment, correct selection of the required ozone doses, duration of the course of treatment and resulting evaluation of its efficiency. In this respect it is necessary to develop and introduce highly effective modern technologies of diagnosing the diseases into clinical practice.

Since considerable a number of different current methods for determining blood AOA exists, selection of the most adequate and appropriate systems of diagnostic laboratory tests has become an urgent problem. The methods, based on the phenomenon of chemiluminescence, are considered to be one of the most up-to-date and quick [5, 5, 7].

The aim of the research is to investigate blood plasma AOA of the UGI patients using chemiluminescence method and recently synthesized ether of acridine carboxylic acid as a luminescent agent [8]. The suggested new method for determining the antioxidant activity of blood using acridine salt [9] permits to calculate the so-called rate constant of quenching plasma luminescence, which is an integral feature, responsive for the presence of all the possible antioxidants in the organism (proteins, low molecular compounds). Thus, this method makes it possible to gathe the most exhaustive information on the spare capabilities of the antioxidant system of the patient organism.

The research deals with studying the influence of the ozone therapy procedures (intravenous injection of the ozonized physiological saline (OPS) and extracorporally ozonized blood (BAGOT) into the organism) on the patient blood plasma AOA.

The following three schemes for blood ozonization has been applied.

Scheme 1. Injection of only OPS with gradually increasing ozone concentration (O_3) in the solution from 2 up to 10-20 mg/l.

Scheme 2. Multi-step thrice-repeated injection of OPS with gradually increasing concentration of O_3 in the solution from 2 to 4 mg/l + BAGOT (while gradually increasing concentration of O3 in the solution from 10 to 25-30 mg/l).

Scheme 3. Multi-step injection of OPS (concentration of O_3 was 2-4 mg/l) + BAGOT (with gradually increasing concentration of O_3 in the solution from 10 to 20-26 mg/l and subsequently lowering it down to 10 mg/l), when the increment of increase in ozone concentration was 3±1 mg/l.

The influence of the applied procedures, irrespective of their type (OPS only or combinations of OPS and BAGOT), on the specific rate constant of quenching of blood plasma chemiluminescence (K_{CL}) of patients with urogenital infections has been found to be of similar nature. The first procedure of the OPS injection into the blood bed resulted in a decrease of the K_{CL} index, which demonstrated a rise after increasing the number of the performed procedures, and by the end of the course of treatment this index either reached the original level or exceeded it.

Application of the OPS only during the whole course of treatment (scheme 1) is characterized by a relatively lower efficiency as compared with combined treatment. When performing the first three procedures (content of O_3 was

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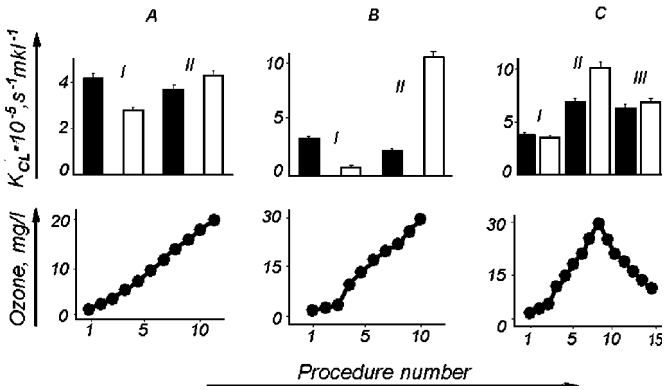

Fig. 1 illustrates the influence of ozone therapy procedures on the on the total blood plasma AOA of patients with UGI

A (upper): the influence of the intravenously injected ozonized physiological saline (Scheme 1) on the total blood plasma AOA of the patient M. (male, aged 55, chronic prostatitis): I – injection of OPS (2 mg/l); II – injection of OPS (10-12 mg/l);

A (lower): scheme of blood ozonization with physiological saline;

B (upper): the influence of combined OPS and BAGOT procedures (Scheme 2) on the total blood plasma antioxidative activity of the patient A. (male, aged 21, urogenital infection): I – OPS, 2 mg/l; II – 3 OPS procedures (2-4 mg/l)+BAGOT (10-20 mg/l);

B (lower): scheme of blood ozonization: procedures 1–3 – OPS; procedures 4–10 – BAGOT;

C (upper): the influence of combined OPS and BAGOT procedures (Scheme 3) on the total blood plasma antioxidative activity of the patient L. (female, aged 26, urogenital infection): I – OPS (2 mg/l); II – BAGOT (25 mg/l); III– BAGOT (15 mg/l);

C (lower): scheme of blood ozonization procedure: procedures 1–3 – OPS; procedures 4–15 – BAGOT;

■ – prior to the procedure; ☒ – after the procedure.

2-4 mg/l) total blood plasma AOA of patients was slightly reduced. Restoration and activation of the antioxidant activity was reported only by the end of the course. Step-by-step application of the OPS and BAGOT procedures exercised a stronger positive action on the blood plasma AOA. In several cases the level of AOA was more than three times increased compared with the original values.

At the same time, when performing BAGOT procedure according to scheme 3, the stage of lowering the level of O_3 in blood was not accompanied by a growth of the AOA, that testifies the direct dependence of the total AOA on concentration and amount of ozone, dissolved in blood.

A comparative analysis of the plasma AOA after completing the course of treatment for various patients has shown that in spite of the dependence of the ozone therapy efficiency on the individual tolerance of patients, their immune statuses, severity of occurrence and stage of disease, sex and age, total regularities of changes in the AOA dynamics throughout the whole course of ozone treatment remain intact. On average, the response of blood plasma antioxidant system of female patients to injection of the ozonized physiological saline or autoblood was manifested weaker (K_{CL} = (6.96±0.16)$10^{-5}s^{-1}mkl^{-1}$) comparing with male (K_{CL} = (7.06±0.22)$10^{-5}s^{-1}mkl^{-1}$), (P<0.05) patients. This may be due to the availability of much developed compensatory mechanisms of the female organism. At the same time, young patients demonstrated the most active response of blood antioxidant system to the applied OPS or BAGOT procedures. The authors also have reported about the dependence of the efficiency of the applied therapy on the original level of blood AOA and the amount of blood-injected active forms of oxygen (O_3), that proves the importance of O_3 concentration in increasing the AOA activity of the patient organism.

The value of blood plasma AOA, obtained due to the original technique, has been compared with the traditionally used LPO indices, characterizing the extent of injuries of cell membranes. After the courses of ozone therapy, particularly BAGOT, the authors observed most considerable decrease of the content of the LPO products in blood plasma: the level of diene conjugates has decreased from 19,7±2,36 to 8,2±1,27 nmol/l (P<0,05), the level of malone dialdehyde has decreased from 20,6±1,7 to 15,2±1,24 nmol/l (P<0,05), the level of Schiff's bases has decreased from 78,8±4,2 to 36,2±3,78 conventional units (P<0,05) and the level of peroxidase C has decreased from 80,62±3,47 to 62,35±1,23. The intensity of Fe^{2+}-induced blood plasma chemiluminescence rapid was significantly reduced from 134,2±6,3 to 81,5±7,2 pulses/360 sec/ml/. The H_2O_2-induced blood plasma chemiluminescence rapid was reduced from 1327±102 to 1012±93 pulses/360 sec/ml, that reflects the dynamics of summary amounts of fatty acid hydroperoxides. Such a strong regulation of the LPO processes intensity by ozone therapy is due to strengthening of the systems of antioxidative and antiradical [5] defense. A significant decrease in the tension of the antioxidant system was further verified by the significant lowering the content of glutathione in blood plasma from 9,23±0,36 mg% to 6,2±0,32 mg%, and of SH–groups – from 70,84±0,52 mg% to 63,6±1,7 mg%.

The investigations, which were conducted, demonstrated that in spite of the ozone inhibiting influence at the initial stage, by the end of the treatment course, the intravenous injections of OPS or ozonized autoblood exercise a stimulating effect on the plasma AOA. The results obtained strongly correlate with the data according to which the ozonized autoblood intravenous injection produce a stronger therapeutic effect, compared with OPS, what is connected with the serum proteins increased production [4]. As it was reported [4], the blood plasma protein spectra changes may be considered as one of the mechanisms of ozone therapeutic action upon the organism. The plasma AOA is realized by means of low molecular compounds (tocopherol, uric acid, ascorbic acid, SH-amino acids, carboxylic acids, nucleic acids, peptides, etc.) and proteins (ceruloplasmin, transferrin, albumin, extracellular SOD, Se-containing glutathione peroxidase, some enzymatic proteins, etc.), the contribution of which into the blood plasma antioxidant status could be as high as 55-72 %. That is why AOA stimulation, observed by the ozone therapy course end, relates to an increase in the plasma antioxidant capacity, which is connected with the content rise of certain proteins, responsible for its antioxidative properties, including transferrin and albumin [4].

The results obtained for dynamics of patients blood plasma total AOA allow to conclude that ozonides and biomolecule oxidation products, injected into the organism during the first procedures, are used for the antioxidant defense of the injured organs and tissues restoration by means of the protection from protein-antioxidants intracellular destruction. And by the end of the ozone therapy course (10-12th procedure), when the antioxidant defense of the organ was restored, the authors observed the total AOA features growth. The original chemiluminescent method for blood plasma AOA determining, which uses the ether of acridine carboxylic acid, allows to evaluate the ozone therapy efficiency and to perform its timely correction.

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Reflexology as the way of lessening of vegetative syndromes in the process of treating of cerebral spastic infantile paralysis and other affections of central nervous system among children

(Based on experience of using contact cuprum-therapeutics (authoring) and vacuum therapeutics with magneto therapy elements)

Valery Kudryavtsev

Dr. Valery Kudryavtsev

Reflexologist of the highest level of proficiency

The urgency of developing of competent methods of reconstructive therapeutics in the case of such a hard pathology as cerebral spastic infantile paralysis is extremely important nowadays. There are many reasons for that as well as obstacles. In spite of the difficultness of disease, recourses of reconstructive therapeutics are rather big. The personal skill of the author of this article indicates it. In the process of working as the reflexologist with sick children over the time of ten years, certain skill of using nonmedicamentous methods of different diseases treatment including cerebral spastic infantile paralysis has been accumulated.

The vegetative imbalances in such pathological statuses are always very marked and, as a rule, their therapeutics is much laboured because of unbalance of all organism systems. Non- traumatic, pain reduction and non - invasiveness of using methods are first-priority in the work of the author. Among them are cuprum-therapeutics and vacuum therapeutics. The first of them is authoring in the pediatric practice. – Authoring certificate and Patent. The second one is long-lasting beneficial vacuum therapeutics practicum.

On the assumption of pathogenesis of cerebral spastic infantile paralysis and other prenatal infantile affections of nerve system cuprum-therapeutics was offered to use. The role of copper in the metabolically processes of human organism became the solid argument in such therapy success. This irreplaceable microelement plays a key role in many catalytic processes. (Report of the author on the 8th Congress in Hanover.)

Applications of copper plates the certain zones by the complex treating of cerebral spastic infantile paralysis used according to author's specially developed programs give a beneficial result in 87% of cases. (3-years result.)

Vacuum therapeutics also has shown its high-effectiveness. It is based on the holomorphy of acting of this technology and the vivid historical skill of using. Only infant organism-adapted cans with special heads and built – in magnets are used. This method was developed according to efficient rules of Reflexology and pediatric peculiarities.

Effectiveness is 78%.

In the conclusion the author summarizes saying that, the implementation of his method of such a complicated pathology treating will give a good opportunity to improve the patients' condition for many parameters especially in decreasing of vegetative dysfunctions.

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Antistress color correction and perspective of its applying

Alla M. Lugova

Corrective health-improving color technologies are very important in the system of modern health care. Antistress Color Correction is one of the most effective technologies.

Antistress Color Correction (ACC) is a new effective method of complex color therapy and color correction, developed by the doctor of medical science, the psychologist-psychotherapist, the leader of courses A.M. Lugova. It can be applied in medicine and psychology. Novelty, uniqueness and efficiency of the method is confirmed and protected by three Russian and one international patents. Antistress Color Correction is a way of correction psychoemotional conditions including:

- The estimation of actual (current) psychoemotional state.
- Analysis of individual peculiarities of a person and his stress stability.
- Testing and correction the health level using irido code (A.M. Lugova method). It can be applied widening the possibilities of the method.
- The situational and typical choice of color (A.M. Lugova method on the basis of which Antistress Color Correction has been created).
- Complex affects by color through the visual analizator: visual color impulse correction by special apparatuses and color correction combinations.

This method gives a choice to choose the color and select color correction combinations for complex color therapy taking in consideration the current psychoemotional state, individual peculiarity of a person and his stress stability.

Visual color impulse correction (VCIC) is the influence by electromagnetic impulses of the visible spectrum through a visual analyzer on the person. VCIC is carried out by means of special glasses with radiator sources of optical radiation and the block of conducting of light impulses. Optimum color and rhythmic components of apparatuses VCIC are the mortgage of affective influence. They allow to make procedures to patients in view of individual perception of color and rhythm. The apparatus «ASIR» possesses broad functional possibilities; it can be applied taking in consideration individual peculiarities of color and rhythm perception. The method of creating such programs for different sicknesses is learned at the author's courses by A.M. Lugova «Antistress Color Correction». There are full time and distance teachings. The listeners at the courses are acquainted with other apparatus. Some of them can be applied in everyday life.

Studies by different authors shoed that visual color impulse correction is high effective, safety, economic, comprehensive, method is combined with other methods of treatment. In the first instance VCIC is applied for correction actual psychoemotional state. The method is the most effective for prophylaxis and treatment of neurotic, psychosomatic disorders and eye diseases.

Visual color impulse correction can be appointed in the form of separate sessions of relaxation at stress and 10-14 day courses for correction current psychoemotional condition and sight prevention and correction neurotic and psychomatic frustration. For definition of rhythms of the visual analyzer which often happens to be broken at psychoemotional and visual infringements, special glasses have been developed for research of rhythms of visual perception in visual color impulse correction. These glasses can be used before appointing ACC and after carrying out the medical course. The given research gives a chance to find infringements of rhythms of visual perception and to estimate efficiency of ACC at their repeated definition.

Color correction combinations are relaxing, toning up and mixing, they are harmonious combinations of colors to the optical degree of their clarification or blackout for visual influence in polygraphic or electronic kind, and also interior and clothes. For a situational and typological choice of color, selection of color correction combination and their further usage the Atlas of antistress color correction tables has been developed. It includes tables for color testing, color correcting circle (12 sectors, 108 segments) and 204 color correction combinations (on 17 for each of 12 pure sated colors of color correction circle).

Antistress Color Correction is affective in prevention treatment and rehabilitation of neurotic and psychosomatic frustration, harmonization of the individual and interpersonal attitudes, increases stress stability and adaptable opportunities of organism.

Antistress Color Correction can be wide applied in Medicine and Psychology. In future it can be used in sports, in medical and psychology sports according to the teaching proposed by A.M. Lugova. ACC can be wide applied in educational institutions in the prevention and correction of visual, emotional and behavioral disorders in children and teens, as well as to harmonize the individual..

Dr. Alla M. Lugova

Doctor of Medical Science, doctor of vegenerative medicine, psychologist-psychotherapist, author of the method of Antistress Color Correction. For 23 years she has been working at science and pedagogical activity on iridology and color therapy, leader of courses. Author of 30 publications, 5 educational methods textbooks, 4 monographs, 5 patents, a number of methodics on iridology, light therapy and colorz therapy.

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Autoimmune thyroiditis - an ancient approach of traditional Chinese medicine to a modern disease

Camilla Luzina[1], Niu Xin[2]

Traditional Chinese Medicine (TCM) has a wealth of experience in treating autoimmune diseases, such as autoimmune thyroiditis (AT), for which it thoroughly explains its pathogenesis. TCM also expounds on the mechanism of acupuncture sanogeneticaly from the standpoint of the ancient natural philosophy.

Chinese medicine treats the human body holistically, taking into consideration the unity of body and spirit and their relationship to the environment. Chinese Medicine appears as a proto-scientific system of health observations and practices based on a syndromatic classification of disease, using two elemental dynamic-processes pattern categorization schemes: a non-hierarchical and combinatorial inhibiting–activating model (Yin-Yang), and a hierarchical and associative five-parameter semantic network (5-Elements/Agents).[1] By challenging the classic theories of western medicine, of which the ultimate goal is to combat symptoms and diseases, new options for thought may be found. For Chinese Medicine, a symptom or disease is a sign of imbalance derived from and affecting the whole body and indicates that other aspects of the patient's life need evaluation as well, not just the apparent organ or system affected [2].

Traditional Chinese medicine treatment of autoimmune thyroiditis has a long history. Treating both hypothyroidism and hyperthyroidism, it is important to notice that in literature hyperthyroidism is mentioned more often. Before reviewing the latest studies, let's try to track the disease and its symptoms back to the first records.

There are no exact name records of this disease to be found in ancient medical recordings. But in the 3rd century BC, the ancient book 《诸病源候论》"General Treatise on the Causes and Symptoms" of Disease describes a diffuse painless thyroid enlargement, with hard texture on the neck as the clinical manifestation, that can be classified under autoimmune thyroiditis. Chinese medicine names it "gall disease", 瘿病 yingbing. The relation to emotional state was also described in ancient China. The book "Recipes for Saving Lives"《济生方·瘿瘤论治》曰："夫瘿瘤者，多由喜怒不节，忧思过度

says: "patients with gall decease can easily become furious, worry too much".

Also, the explanation of clinical manifestations were mentioned in the Orthodox Manual of External Diseases 《外科正宗·瘿瘤论》云：："夫人生瘿瘤之症，非阴阳正气结肿，乃五脏淤血、…痰滞而成。where the symptoms were explained as a result of disharmony between Yin and Yang leading to nodule, edema, and phlegm stagnation.

As we see the symptoms were described and treated by the Chinese doctors long before the disease was clearly diagnosed in modern medicine.

However, according to Dr. Dharmananda, until the past fifty years, thyroid disease could not be definitively diagnosed in China; rather, Chinese doctors could only detect a certain set of symptoms to be treated and could palpate any moderate or large nodules in the area of the thyroid gland, undeniable, but fact. The syndromatic classification is a basis of traditional Chinese medicine. [4] Luckily now, objective measures, such as altered levels of thyroid hormone, can give a clue as to the site of the disease and can further elucidate the influence of various therapeutic measures that might be applied.

Dr. Camilla Luzina

Neurologist, graduate of Sechenov Moscow Medical Academy; Currently post-graduate student at the Beijing University of Chinese medicine, is reading a course on neurology , Interested in integrative medicine, thyroid research, the TCM ; has taken part in a number of national conferences and international congresses; Has publications in Chinese and Russian.

Traditional diagnostic indicators

In the last 20 years there were numerous researches dedicated to diagnostic and treatment of AT. Commonly, autoimmune hypothyroidism is classified into 4 types: yang-insufficiency of the spleen and kidney: yang-insufficiency of the heart and kidney; yang-qi failure; the type of deficiency and loss of kidney essence. (Tao Chunxiang 陶春祥 Journal of Traditional Chinese Medicine 2008; 28(3):231-232) [5])

The main cause of hypothyroidism is Yang Deficiency in which the body's function to warm, motivate, and transform is inadequate. The primary organ systems include the Spleen and Kidney, and the Heart organ system becomes more involved in the advanced stage. [6] According to Dr. Wei Liu In the pattern of Yang Deficiency with Spleen and Kidney Deficiency, the key symptoms are: lassitude; sleepiness; poor memory; dizziness; ringing in the ears (tinnitus); weakness of the lower back and knees; aversion to cold; dry skin; dry hair; constipation; edema; impotence (men); irregular periods (women); pale, puffy tongue body with tooth marks along the edge; white, sticky tongue coating; and a pulse that is deep and thin or deep and slow. In the pattern of Yang Deficiency with Heart and Kidney Deficiency, the characteristic symptoms are: heart palpitations; chest congestion and pain; sleepiness; feeling cold; pale, tender tongue body with a white, slippery coating; and a deep, slow pulse.

Three patterns of Yin Deficiency are differentiated for

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hyperthyroidism: Kidney Yin Deficiency with Excess Heat; Heart/Liver Yin Deficiency; and Heart/Kidney Yin Deficiency. In the pattern of Kidney Yin Deficiency with Excess Heat, typical symptoms are: enlarged, soft, smooth thyroid; anxiety; anger; aversion to heat; flushed, warm face; dry mouth with a bitter taste; increased appetite; bulging eyes; tremor; increased volume of bowel movements, a red tongue body with a dry, yellow coating; and a wiry, rapid pulse. In the pattern of Yin Deficiency with Heart and Liver Deficiency, the symptoms are: enlarged, swollen, soft, smooth thyroid; heart palpitations; anxiety; insomnia; increased appetite with weight loss; dry throat; a red tongue body with a yellow tongue coating or no coating; and a thin, rapid pulse. In the pattern of Yin Deficiency with Heart and Kidney Deficiency, the characteristic symptoms are: heart palpitations; chest congestion and pain; sleepiness; feeling cold; pale, tender tongue body with a white, slippery coating; and a deep, slow pulse. [7]

Chen HP, He JS, Hu GS. [Analysis on the traditional Chinese medicine syndromes of the patients with autoimmune thyroid diseases. Changes in the thyroid and immune functions in 109 cases] / / Zhong Xi Yi Jie He Za Zhi. 1990 Sep; 10 (9): 538-9, 517. The authors found that patients with syndrome of deficiency of Yin content of T4 and T3 were higher, TSH - below normal levels. Patients with Yang deficient syndrome, the levels of T4 and T3 were lower, and TSH - above the normal range. The percentage of OKT 4 cells and the ability of lymphocytes to autorecognition at thyroid specify (Yin deficiency syndrome) have been reduced, while hypothyroidism (Yang deficient syndrome) - elevated. Moreover, in both situations, the content of autoantibodies was increased.

Acupuncture/moxibustion

In the past years there were numerous researches dedicated to acupuncture treatment of autoimmune thyroiditis. But in my opinion it is important to admit, that a great number of researches in China, and many other counties mainly use herbal treatment for AT. [4], [8]- [10] Acupuncture as an individual method has not been very widely used. So far it is only on a path of finding solid scientific basics, but the results are predominantly positive. Acupuncture can regulate on different levels the autonomic nervous system, hormone, and neuropeptide release to help control metabolism and may aid in regulating the immune system.[11] [12] As well as regulating the emotional state of a patient.

From the classical books of traditional Chinese medicine the most common points are recommended. Comprehensive Guide To Chinese Herbal Medicine mentions the following points for hyperthyroidism: naohui (TB13), zusanli (ST36), hegu (LI4).

The Treatment of Knotty Diseases with Chinese Acupuncture and Chinese Herbal Medicine lists the following for "senile hyperthyroidism:" guanyuan (CV4), shenshu (BL23), mingmen (GV4).

This source also lists moxa points: guanyuan (CV4), qihai (CV6), mingmen (GV4), and shenshu (BL23) for cases of impairment of yin affecting yang.

Acupuncture can be used in conjunction with conventional medical treatment, or it can be the prevalent treatment. [13] According to the latest researches, acupuncture can be successfully used to treat autoimmune thyroiditis. 51 cases of hypothyroidism were reported by Zhang Yaohua. As the results show 67 % (32 cases) were cured, 19,6 % markedly effective after a long term treatment course.

The research in Russia also shows positive results. Corporal acupuncture and ear acupuncture were used primary to treat autoimmune thyroiditis. "Irrespective of its initial index, thyroid status had a tendency to normalize with all the patients. 20% of the patients stopped receiving hormonal therapy, 77 % of the patients could reduced the doses of the hormonal medication three times. In all the cases the level of anxiety and depression diminished. In 90% of the cases the quality of life improved. "[14]

Conclusion

The general methodology of classical acupuncture, based on the philosophical concept of Yin-Yang and Wu Xing fully consistent with the synergy - evolutionary paradigm of modern science and the provisions of the modern systems theory. The results of theoretical analysis allow us to consider the concept of Yin and Yang as the prototype of the dialectical law of unity and struggle of opposites. As a naturalistic interpretation suggested to consider the concept of Yin and Yang from the standpoint of the hypothesis of an integral regulator of the continuum, the biochemical component of which corresponds to the category of Yin and biophysical - Yang categories.

Acupuncture is aimed at the recovery of broken psychosomatic relationships at biochemical as well as biophysical levels .But the mechanisms of acupuncture need to be more deeply studied in order to fully explain its therapeutic effects.

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Acupuncture – altenative approach to subclinical hypothyroidism correction. Ongoing research

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Background & Introduction

The replacement therapy (RT) of subclinical hypothyroidism (SHT) with individually selected doses of levothyroxine (L-T4) which provides supporting the normal level of thyrotropin hormone (TTH) is considered to be "the gold standard" of modern endocrinology. The issue of the appropriateness of RT at subclinical hypothyroidism (SHT) has been the subject for discussion at large for more than 30 years already [1].

SHT has been initially defined as a laboratory phenomenon stipulated by the introduction of highly-sensitive tests for the hormone level in blood plasma into practice. Further research has shown that this "laboratory phenomenon" may be accompanied with yet nonspecific but rather manifested symptomatology which results in life quality decrease [2], that, of itself, requires medical aid. In addition, the advocates of RT application at SHT give reasons with the data of the possibility for its transformation into clinically overt hypothyroidism. Against a SHT background there is the increase of the risk for the genesis of mental and psycho-emotional dysfunctions[3 - 5], dyslipidemia and cardio-vascular pathology [6], oncological diseases [7], reproduction abnormalities [8, 9], a number of other diseases and pathological states. Such a wide range of possible risks is probably associated with mitochondrial dysfunctions at SHT [10]. However, even individually selected RT does not always provide the TTH level normalization, and 10% of the patients with its normal level feel sick [11].

The above circumstances stipulate the urgency of the search for approaches to the SHT problem solution that are alternative to RT. The issues of acupuncture (AP) application in the treatment of thyroid gland diseases are covered in the contemporary medical literature considerably less extensive than AP treatment of other illnesses and syndromes. For instance, on the whole, on 09.12.2010 in PubMed the search words «acupuncture treatment» found 15147 sources, the words «acupuncture low back pain», «acupuncture bronchial asthma», «acupuncture gastrointestinal», «acupuncture

Table 1. The most widespread complaints and symptoms at the start of treatment (n – absolute number of the patients with above complaints and symptoms, N (=27) – total number of the patients)

No.	Complaints and symptoms	n (n/N•100)
1.	Pain syndromes (arthralgia, fibromialgia)	21(78)
2.	Asthenia, rapid fatigability under exercise and psychic stress	20(74)
3.	Apathy, indifference to the ambient situation, drowsiness	20(74)
4.	Poor memory, delayed response, disability to concentrate attention	15(55)
5.	High nervousness, irritability	14(52)
6.	Edema, increased body weight, constipation	13(48)
7.	Chills, low tolerance of cold	12(44)
8.	Sensitive skin, fragility of nails and hair	6(22)
9.	Hoarse voice	5(18)

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Table 2. Changes of complaints and symptoms during two courses of treatment. See the explanations in the text.

Complaints and symptoms (No)	Course I (n=27)		Course II (n=20)	
	before	after	before	after
1	21(78)/5,2	2(7)/1,5	13(65)/3,4	1(5)/2,0
2	20(74)/6,7	6(22)/3,2	12(60)/5,0	4(20)/2,0
3	20(74)/6,7	3(11)/1,0	8(40)/3,8	2(10)/2,4
4	15(55)/4,9	3(11)/2,4	6(30)/3,5	1(5)/2,0
5	14(52)/3,7	5(18)/2,5	7(35)/2,9	2(10)/2,0
6	13(48)/3,9	6(22)/2,3	2(10)/1,0	0(0)/0
7	12(44)/5,0	0(0)/0	2(10)/1,0	0(0)/0
8	6(22)/3,1	2(7)/1,5	0(0)/0	0(0)/0
9	5(18)2,9	0(0)/0	0(0)/0	0(0)/0

thyroid» и «acupuncture thyroiditis» found - 379, 328, 223, 50 and 6 sources respectively. In 50 entries found with the search words «acupuncture thyroid» there are described positive results of AP in the treatment of both hypothyroidism and hyperthyrodism. There was found no information about the appropriateness of AP application at SHT that was the reason for the implementation of the present research.

The research objective –

investigation of the acupuncture effect on the symptoms, the TTH level and the life quality of the patients with subclinical hypothyroidism who do not receive the RT.

Records and methods of the research

The records of 27 women patients at the age of from 25 up to 57 years who appealed to Sin Ya Chju centre primarily for the care of the present pain syndromes and concomitant neurasthenic symptomatology have been included. On the basis of the initial examination results and the TTH level increase at the normal level of the free T4 the "SHT" has been diagnosed.

All patients received course treatment of 10 – 12 AP sessions carried out every day or ever other day. The treatment procedures included AP of the corporal, auricular, scalp and carpal reflexogenic zones according to the present symptomatology and pursuant to the rules of traditional Chinese medicine. Besides that, the needles have been applied in the zone of the skin projection for thyroid gland. In addition, the Gua Sha technique has been used in the paravertebral zones of the cervical and thoracic spine relating to the vegetative innervation of thyroid gland. 20 of 27 women have received 2 courses of treatment with 3-4 months intervals between the courses.

Before the beginning and after the end of every course of treatment a thorough analysis of the patients' complaints and symptoms was performed. The changes of the specific complaints were assessed percentage wise in the group

Table 3. Dynamics of TTH levels in the process of treatment

Course of treatment	Dates of the tests		
	1 (mME/l)	2 (mME/l)	3 (mME/l)
I (n=27)	8,9 ± 2,3	4,2 ± 1,1	2,3±0,3*
II (n=20)	4,9 ± 1,2	2,0 ± 0,9*	1,5 ± 0,4**

*Notes: Dates of the tests: 1 – before the beginning of the course of treatment, 2 – just after the course of treatment, 3 – in a month after the completion of the treatment course. * - (p≤0,05), ** - (p≤0,01) significant differences in comparison with the data before the treatment.*

and on the basis of the average value of the points given by the patients to the complaints' manifestation in accordance with the visual-analogue scale from 0 to 10 points. The level of anxiety and depression has been defined according to the questionnaire adopted in Russia for detection and assessment of neurotic states (K.K. Yahin, D.M. Mendelevich, 2005). The TTH level was evaluated before, right after and a month after every course of treatment. The quality of life was evaluated in accordance with the Russian language version of the questionnaire SF36 (J.E.Ware et.al.,1988) before the first course and 2 – 3 months after the end of the second course of treatment.

Results

At the start of the treatment the patients voiced a wide range of complaints associated with the reason of their appeal for medical aid. Nine of the most widespread complaints are represented in Table 1.

The obvious reason for the highest rating of pain syndromes usually excluded from the typical hypothyroid syndromes is that pain syndromes often constitute the initial cause for medical aid appeal. Low rating of symptoms No 7 – 9, that are usually included into the clinical presentation of hypothyroidism, can be formally explained by the "subclinical" form of the disease. As is known, hypothyroidism symptomatology is nonspecific on the whole, complaints and symptoms No 2 - 5 accompany many nosological forms and pathological states and are comprised by the general syndrome of the disease.

The changes of the registered complaints and symptoms are displayed in Table 2, in which their numbers coincide with the numbers in Table 1. The figures before brackets are the absolute quantities of the patients, the figures in brackets represent the percentage of the total patients' number, the

Table 4. Indexes of life quality before and after two courses of treatment

Scale SF36	before	after
Physical Functioning	53,2 ± 2,1	70,0 ± 3,5
Role of Physical Factors	39,5 ± 1,5	77,1 ± 3,2
Bodily Pain	47,7 ± 1,5	78,3 ± 2,7
General Health	45,8 ± 1,7	83,5 ± 3,4
Vitality	46,7 ± 1,9	74,9 ± 3,2
Social Functioning	71,1 ± 2,6	80,7 ± 3,1
Role of Emotional Factors	31,0 ± 1,2	67,8 ± 2,8
Mental Health	75,1 ± 2,0	82,1 ± 2,9
Average value of the points in accordance with all scales	51,2 ± 1,8	76,8 ± 3,1
Δ	25,6	

figures after «/» show the average intensity of the symptoms in the units of the visual-analogue scale.

As follows from the given data, a considerable reduction of the symptoms was observed already after the first course of treatment. All initial symptoms entirely vanished in 7 patients out of 27 women, they felt completely healthy, and that was why they did not need a repeated course of treatment. In 3-4 months other 20 patients began to observe partial reiteration of the initial symptoms which was the reason for performing the second course of treatment. On its end 4 representative hypothyroidism symptoms did not appear at all, and other

symptoms were minimized.

Resulting on the analysis of the questionnaire's data of detecting and assessing neurotic states there were ascertained polymorphic variants of dysfunctions with dominant anxiety-depression manifestations. Before the treatment against the background of 100% asthenic symptomatology clinically evident anxiety and depression were observed in almost 50% of the patients. 33% of the patients had hysteromorphic symptoms as demonstrative behaviour and somatic symptomatology aggravation. After the first course of treatment neurasthenic symptomatology decreased to 35%, anxiety and hysteria lowered to 18 and 22 %% respectively, and clinically evident depression was not revealed at all.

On the eve of the second course of treating neurasthenia, anxiety and depression were observed in 40, 30 and 10 %% of the patients respectively. Though less evident, hysteromorphic symptoms were revealed in the same number as after the completion of the first course of treatment. On finishing the second course of treatment, clinically significant evaluations of neurasthenia, anxiety and depression were not found. The number of patients having hysteromorphic symptoms did not change, but their evidence decreased. Additional test (test MMPI) displayed that the cases of minor changes of neurotic manifestations were related to the personal qualities of the patients.

The results of TTH levels' detection are displayed in Table 3.

Despite double reduction, just after the first course of treatment, the TTH level did not reach conventional normal values (0,4 – 4,0 mME/l). Its decrease to the normal limits took place within a month after the completion of the course. However in 3-4 months (before the beginning of the second course) an average insignificantly supernormal TTH level was observed once again. Just after the second course it became normal and kept declining during the consequent month.

The improvement of clinical symptomatology and TTH level resulted in the positive changes of the patients' life quality indexes (Table 4).

As a result of the given treatment a reliable increase of the indexes was registered according to all SF36 scales excluding «Mental Health», the initial level of which practically did not differ from the typical normal values. The average initial level of the life quality index based on all scales increased by 25,6 points, having reached the typical level for healthy people which is equal to app. 80 points.

Discussion.

In the present research we have showed the results of following-up 27 patients who appealed for medical aid largely because of pain syndromes. Given symptomatology could correspond the diagnoses «fibromialgia», «chronic fatigue syndrome» and a number of other diseases. In connection with the revealed isolated TTH level increase these diagnoses had to be supplemented with «SHT» diagnosis. Resulting data displayed that already after the first course of treatment 7 out of 27 patients did not need the continuation of the treatment.

In 3-4 months 20 patients expressed their wish to take one more course of treatment. The indexes of clinical state and TTH level during the second course showed more evident improvement in comparison with the first course. Monitoring the condition of some patients' of the group continues. In addition, monitoring two more groups of hypothyroidism patients – those receiving and not receiving a replacement therapy. That's why our study is called ongoing research. The name of the disease - «subclinical hypothyroidism» - formally excludes a positive answer to the question that is urgent for today's thyroidology - to treat or not treat? [1]. A laboratory phenomenon of isolated TTH level increase which is not accompanied with clinical presentations, but is a factor of their genesis risk. It requires no treatment, but preventive correction. Preventive measures, by definition, exclude RT, they imply the use of more physiological approaches.

As the present research has shown, AP can be applied as such. There are evidences of goiter treatment (yin bin) - 瘿病 in the treatise "Huan-Di Nei Tzin" – "The Yellow Emperor Canon" dated to 3 - 2 cc. BC. The development of yin bin was explained by "Ci stagnation". In accordance with the basic goiter symptoms the treatise describes main organs "responsible" for them – kidneys (congenital Ci) and pancreas gland (evoked Ci). The recommendations for the appropriateness of the tonic effect on the corresponding acupuncture channels are based on these notions. The observed dysfunctions of thyroid status and clinical presentations of hypo- and hyperthyroidism are currently interpreted basing on the Yin-Yan balance [12]. In addition to that the improvement of our patients' condition in the course of treatment can be explained in the modern life science perspective.

The interactions of sympathoadrenal and thyroid systems coordinated on the level of hypothalamus and peripheral tissues take part in providing a wide spectrum of normal adaptive reactions in hematothermal organisms. Disruptions of this coordination are one of the important components of chronic stress genesis. Hypothyroidism is featured with adaptive response suppression [13].

Before treatment the increased levels of anxiety and depression in the patients included into the present research were significative of the chronic stress state. In his early works Hans Selye informed that thyroid gland functional activity is increased under short-time stress and suppressed under chronic stress. AP procedures, especially cranial AP carried out through achieving the foreseen sensations are a short-time mild stress for the patients. According to H. Selye such short-term stress effects can limit hypothyroid reactions attributed to chronic stress. Stress-limiting action of AP is provided through mobilization of natural central and local antinociceptive systems of an organism and presented by a wide spectrum of treatment and preventive effects [14]. As the results of the first stage of our ongoing research have shown this spectrum include acupuncture prevention of possible negative SHT consequences.

Conclusion

The results of the research give the reasons for the considering AP as a possible alternative replacement therapy and an innovative approach to the solution of SHT problem.

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Psychogenic, somatoform and functional itch: heterogeneity or overlap of the phenomenon?

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Introduction

Itch or pruritus is one of the most common symptoms in dermatology. About 35% outpatients of the dermatological clinic suffer from itch (Alexander H., 2005). In general population it occurs within prevalence from 8.8% to 13.9% (Wolkenstein P., 2003, Dalgard F., 2005, Halvorsen J.A., 2009). Itch accompanies skin diseases (atopic dermatitis and urticaria) in 100% of cases (Weisshaar E. et al., 2009), psoriasis in 87% of cases (Yosipovich G., 2000; Krueger G., 2001), herpetic infection in 58% cases (Oaklander A.L. et al., 2003) as well as systemic diseases (chronic renal or liver failure, lymphoproliferative diseases, oncological process) and psychiatric disorders.

Itch unexplained by any dermatological or somatic cause is considered as psychogenic or functional and equivalent to somatoform one (Harth W. et al., 2006; Misery L., Alexandre S., 2007). Somatoform pruritus is usually attributed to undifferentiated somatoform disorder (DSM-IV-TR; 300.81), that could include not just «sine materia» symptoms, but also cases when physical complaints are in excess of what would be expected from the existing medical condition, i.e. «cum materia». Psychogenic itch is diagnosed in 6.5 % of outpatients of dermatological clinics (Stangier U., Gieler U., 1997) and implicates relation of pruritus exacerbation with psychosocial stress exposure.

Objective

of the study was to evaluate complex clinical structure of somatoform itch in order to distinguish its psychosomatic variants.

Methods.

Psychopathological and dermatological observation by dermatologist and psychiatrist of 40 patients with itch (24 women, mean age - 34,6±11,3 years) in the dermatologic department. Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxious and depressive symptoms.

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M.D., dermatovenerologist, Ph.D.-student of dermatological department of I.M. Sechenov Moscow State Medical University, studied in clinic for Dermatology and Allergology Philipps-University in Marburg in 2007-2008. PhD thesis Theme"Psychogenic itch: aspects of clinical systematics, complex therapy and prophylaxis" under supervision of professor of dermatological department A.N. Lvov in collaboration with research worker of department for psychiatry and psychosomatics, psychiatrist Phd Romanov D.V.), the co-author of 22 research papers and repeated laureate of competitions for best scientific work among young scientists, was awarded with the medal of the Russian Academy of Medical Scientists for the best scientific work in 2008, member of Moscow society of dermatovenerologists, european academy of dermatology and venerology and international society of dermatology

Results

Examined subjects were divided into 2 groups: somatoform itch «sine materia» or functional (n=26) and somatoform itch «cum materia» (amplifying and mimicking existing dermatological diseases). (n=14).

In the first group without dermatological diseases subjects itch descriptions varied greatly in quality (burning, tingling, stabbing, biting, crawling), localization (generalized, localized) and intensity (up to itch paroxysms). In the second group (atopic dermatitis in 8 cases - SCORAD = 36,7±11,2; psoriasis in 6 cases - PASI = 16,9±4,8) itch was monomorphous and described as just «sensation causing desire to scratch» or burning. The following registered itch characteristics allowed to attribute this variant of somatoform pruritus to «cum mate-

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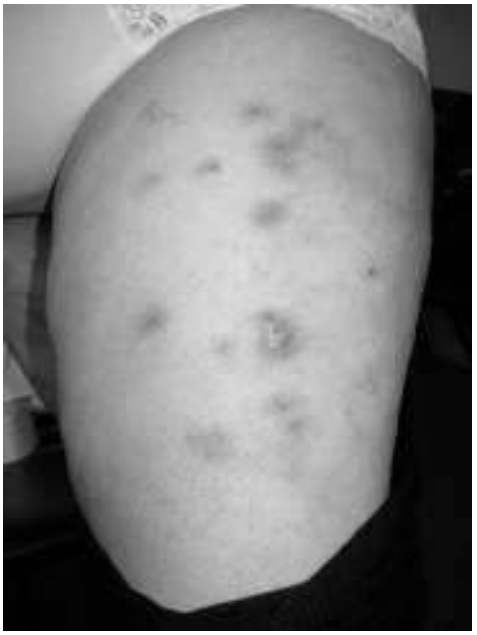


Figure 1 and 2. Self induced skin lesions caused by itch of the first group of patients.

ria» phenomenon and distinguish from typical dermatological itch and «pure» psychogenic pruritus: 1) itch localization greatly exceeding the atopic or psoriatic eruptions areas; 2) itch emerged as a prodromal symptom of psychogenically provoked relapses of dermatoses with typical eruptions only in several days; 3) itch persisted after eruptions totally disappeared; 4) there were psychogenically provoked transient itch flares on a spare skin in dermatoses remissions.


Figure 3 and 4. Amplified itch in patients with Atopic dermatitis (clinical picture of a patient from second group)

In spite of the differences observed patients with these two types of somatoform itch had much in common. There was a high level of comorbid anxious symptoms in both groups with prominent «health anxiety» (HADS anxiety subscale score – 15,4±3,2), but no signs of clinically relevant depression or other severe psychiatric disorders. Psychogenic exacerbations of functional itch were registered in about a half of patients in both groups (46,1% and 50% respectively). Patients of both groups also had other somatoform complains according to life history and/or at the time point of examination: pathological sensations and vegetative dysfunctions. The functional non-skin symptoms could be single and recurrent (pseudosomatic episodes) or manifest in a form of cardiac or gastric neurosis, hyperventilation or irritable bowel syndrome. Also patients of the sample reveled a kind of constitutional somatopsychic predisposition (neuropatic constitution) with symptomatic lability and multiple somatosensory disturbances, which could be considered as a predisposing factor to multiple somatoform complains including somatoform pruritus.

Discussion.

Somatoform itch is a heterogeneous group that includes 2 variants: functional and amplified itch [6]. Nevertheless, diagnose of dermatoses doesn't exclude the possibility of somatoform itch: minimal skin lesions could be accompanied by over-intensive itch in case of psychosomatic disturbances. Psychogenic itch is provoked by stress and can occur in two variants. On the one hand, it could be told about heterogeneity of somatoform itch phenomena, on the other hand – about overlap due to psychogenic provocation, general constitutional features and comorbid somatoform phenomena.

Conclusion. Somatoform itch is a heterogenous phenomenon developing as in a form of «pure» functional condition («sine materia»), as in dermatological itching diseases («cum materia»). Described two variants have common psychiatric comorbidity and constitutional predisposition.

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The significance of osteopathic correction of nasal breathing in children

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Nose is the primary department and "site of entry" of air passage through which inhalable and exhalable air passes. Among other things, nose cavity – is the zone abundant in nerves connected with different humane organs and systems. The nose has the following physiological functions – breathing, protective (reflectory) and resonance, i. e. speech. Nasal breathing disorder, dysfunction of sense of smell and of protective function negatively affect many organs and systems: cardiovascular, breathing, above all intracranial, cerebrospinal, intraocular pressure, cerebral circulation and brain functions, motor and secretary functions of gastrointestinal tract, etc.

The role of cavernous tissue is significant. The rate of congestion and decongestion of cavernous tissue of the nasal cavity provides the optimal quantity of inhaled air, speed of air passage, humidity and air pressure, temperature and other rather important factors of nasal physiology. The cavernous tissue is extremely closely connected with vegetative nervous system and fifth cranial nerve; blood filling of mucus membrane of nasal cavity is regulated by sympatic and parasympatic fiber of the nervous system.

Breathing function of the nose is its main function. Depending on many conditions the nasal cavity either spreads or coarctates at the expense of involution of the cavernous tissue of the nasal cavity, or coarctates as the result of the decongestion of the cavernous tissue of the nasal cavity. As children of early age have rather well-developed concha of cranium their breathing is fulfilled basically through the systemic narrow nasal passage. This circumstance has great significance for the clarification of the reasons for dissonance between insignificant inflammatory process in the nasal cavity and the severity of the general condition of a child. Nasal respiratory malfunction can lead to different malfunctions in children, which includes maldevelopment of the facialis (for example, "adenoid look"), emergence of faryngitis, laryngitis, traheitis and other diseases.

Osmetic function is important as a child lives in the world of many different smells. Smells influence differently the functions of organs and systems of its organism.

Protective and reflectory functions of the nose are rather compound and diverse. In the nasal cavity air gets warm, humified, cleaned up, disinfected. Sneezing, lacrimation are protective nasal reflexes. Warming of the air in the nasal cavity is achieved by having a great number of blood vessels here. If the surrounding temperature is higher than the temperature of the body, then the inhaled air becomes cool. Humifying of the air is achieved by mucus and lacrimal fluid.

Resonatory function of the nasal cavity and paranasal sinuses consist in strengthening of different tones of a voice, what is regulated by the position of the soft palate. Nose and paranasal sinuses as resonators can be "switched on". Switching on and switching off this resonator depends on functional condition of muscles of the soft palate and pharynx. This distinguishes it from other resonators.

Among all mentioned above functions of the nose due to the significant meaning of the nose breathing for the developing organism of a child it should be noted that switching off and even difficulties in nasal breathing negatively affect both the functions of separate organs and systems and the condition of organism on the whole. Malfunction of the nasal breathing reflects on neuropsychic activity, oxidative and restorative processes, blood composition. With this malfunction gas exchange reduces, worsens ventilation of lungs, paranasal sinuses and middle ear, nocturnal urinary inconsistence appears, and newborns can have opithotonos, convulsions even with short-term switching off the nasal breathing.

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The essence of treatment of inflammatory diseases of the nose and paranasal sinuses in children follows from their etiology and pathogenesis, that's why all attention is concentrated on this in treatment. They try to get to normal breathing through nose in most possible short terms, to limit spreading of the process, to prevent development of possible complications. They try to make the therapy saturated, prolonged if needed, including complex of different methods and measures.

The main aim of local treatment is providing free outflow of contents from the nose. Traditionally it is achieved by surgical measures (resection of hyperthophic, polypous concha nasalis, excision of thorns, resection of internasal septum, etc.) or by methods which assist in broadening of natural opening of sinuses (use of vasoconstrictive agents, drainage of sinuses, etc.) or by remedies diluting pus (physiotherapeutic procedures), or in some cases by combination of these methods.

It is necessary to admit that modern methods of treatment have side effects and are not always effective.

Another approach was implemented in osteopathic practice in treatment of acute and chronic diseases of the nose and paranasal sinuses in children of all age groups. In the light of conceptions of osteopathy as a science the reasons of emergence of diseases were analysed. In the result of the analysis it was brought to light that major part of diseases of the nose and paranasal sinuses have in their pathogenesis one reason. It is trauma, most often not in the part of a nose, but trauma of a head or something located lower. As a result hemodynamics interrupts in all craniosacral system, what leads to laboured inflow and outflow of fluids to the head. Stasis emerges in the nasal cavity and paranasal sinuses, what leads to swelling of nasal mucus membrane and emergence of favourable conditions for pathogenic flora.

On the basis of the Institute of Osteopathic Medicine by

Private Practice, Saint-Petersburg, Russia

St-Petersburg Medical Academy of Postgraduate Study research was conducted, where classical (allopathic) and osteopathic treatments were implemented on two groups of children. In the result of the research the following summary was made: allopathic (traditional classical) treatment – is the impact on the symptom of the disease, that's why its effectiveness has temporary character, the causes remain and the disease comes back. Osteopathic treatment is aimed at the elimination of the causes of diseases, mechanical injuries of cranial bones, bones of pelvis, spine, chest, normal equilibrium of membranes of reciprocal tension is restored, blood-, lympho- and liquor-dynamics are improved, i. e. fluctuation of fluids in the organism is normalized and as a result good outflow of fluids from the head and nasal cavity particularly is provided. Normal innervation of the visceral scull is provided. The result of it – is the enlargement of volume of the nasal cavity, normalization of the curvature of the nasal passages, opening of foramen communication of nasal cavity with paranasal sinuses, reducing of volume of mucus tunic and improvement of quality of the mucus. After osteopathic treatment not only nasal breathing improves, but general condition of the organism does, this improvement has steady character in the better way with the course of time.

As appears from the above, to define the reason of the disease of nasal cavity and paranasal sinuses correctly it is needed to do the following: to define correctly the pattern or the position of the cranial bones, notably, those constituent the nasal cavity; to check the condition of commisures between them; to define the presence of intrabone injures; to pay special attention to the tension of membranes of the receptory tension, to define the places of vasoneuropathy; to evaluate the condition of sphenopalatine hole.

To enhance the work of all functions of the nasal cavity it is necessary to eliminate basic symptoms of the disease, i. e. edema and swelling of the mucous tunic, laboured outflow of the exudates. But having not eliminated the cause, it is not effective to treat symptoms. First of all, one should eliminate the stasis and provide innervation of the central and vegetative nervous systems, which have become the consequence of malfunction of the kinetics of the cranial bones. One should restore the dynamics of the structures, which constitute the nasal cavity and paranasal sinuses, thereby provide good drainage of the cavernous tissue of the nasal cavity. And it can be done thanks to osteopathic methods.

Probiotic treatment of irritable bowel syndrome in children

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Abstract

Treatment of functional bowel disorders of irritable bowel-type (IBS) in children remains a difficult task because of a lack of drugs with low adverse event profile. We here report the results of a treatment study in 203 children (66 boys and 137 girls) age 4 to 18 years (mean: 10.5±4.5 years) with typical IBS symptoms with abdominal pain and either predominant diarrhea (n=50), constipation (n=56), alternating stool frequency (n=28) or unspecific pain (n=69). The average duration of symptoms prior to therapy was 175 days. Most (95%) patients up to age 11 were treated with a daily dose of 10 drops of Symbioflor 2 (SF2) (SymbioPharm, Herborn) (cells and autolysate of 1.5–4.5x107 CFU of bacteria of Escherichia coli type), in the elder children 77% received this dosage, while the remaining received a higher dose up to 30 drops/day. Treatment lasted 43 days on average. Results: All patients tolerated the treatment well and without adverse events. The key IBS symptoms (abdominal pain, stool frequency) as well as the other symptoms (bloating, mucous and blood in stool, need for straining at stools, urge to defecate) improved significantly during treatment. Global assessment of therapy by parents and doctors was altogether positive. In summary these data confirm efficacy and tolerability of this probiotic compound in children and adolescents and supplement published data of probiotic IBS therapy in adults.

Introduction

The irritable bowel syndrome (IBS) is a functional bowel disorder and characterized by a number of symptoms including abdominal pain or discomfort and disturbed bowel habits. Other typical IBS symptoms are diffuse abdominal pain, bloating, excessive passing of gas, irregular bowel movements with improvement of symptoms after defecation, and/or the feeling of incomplete evacuation. Morphological abnormalities are missing that sufficiently could explain the symptoms, as are diagnostic criteria and proven pathophysiological concepts; hence a therapeutic concept based on such findings is lacking as well.

The diagnosis is usually based of the recording of the typical symptom pattern, the absence of alarm symptoms, and the exclusion of a number of differential diagnoses. In the present observational study, the recently published diagnostic criteria of the Rome III consensus for IBS have

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At least 1 x per week for at least 2 months abdominal discomfort or pain with 2 or more of the following charactenstics • Improved with a bowel movement • Begin is associated with a change in stool frequency • Begin is associated with a change in stool consistency • No signs of inflammatory, anatomical, metabolic or neoplastic processes that could explain the symptoms

Table 1: Rome III criteria for irritable bowel syndrome (IBS) in children and adults

been applied [1], [2], (Table 1 [1]). This classification was meanwhile also applied to childhood functional bowel disorders [3] and has replaced the older terminology that used "recurrent abdominal pain" as diagnostic label [4].

IBS is a frequent disease in the general population. The worldwide prevalence ranged between 10 and 20% in the adult and adolescent population, and women are more often affected than men. The disease has substantial consequences on quality-of-life of patients and induces high direct and indirect medical costs [5].

For pediatric patients, very few data are available. The recently published children and adolescent health survey (KIGGS) collected – among others – representative data on pain in children age 3–17 years in Germany [6]. In children between 3 and 10 years, "belly pain" was the most frequent pain location, while children age 11 to 17 most frequently reported headaches, followed by abdominal and back pains [7].

Non-medicinal general management strategies including exercises, stress reduction, and relaxation techniques may serve as supplementary options in addition to drug therapy of key symptoms, e.g. regulation of stool consistency, against bloating, spasmolytic therapy and modulation of gastrointestinal motility. Only a few new drug developments have found their way into clinical routine in the last years [8], but most have never been tested in children.

Since a number of years, prebiotic and probiotic therapies have seen a renaissance [9] in clinical use and are most often used in functional gastrointestinal disorders [10]. Their low adverse event profile [11] also supports their use in childhood functional bowel disorders but respective studies are rather scarce [12] – they are mostly used with dermatological and allergic diseases [13].

Symbioflor® 2 (SF2) (SymbioPharm GmbH, Herborn, Germany) contains both living as well as non-living Escherichia coli bacteria (cells and autolysate of 1.5–4.5x107 bacteria) and is – based on current knowledge – effective in the therapy of functional bowel disorders [14]. We here report the open label use of SF2 in 203 children age 4 to 18 with IBS symptoms according to Rome-III criteria.

Initial investigation
- Demographic information (initial, sex, age, height, weight)
- Confirmation of the diagnosis IBS according to the Rome III criteria for children
- Documentation of the type of IBS
- Exclusion of colonic polyps, lactose malabsorption, and sprue
- Start of symptoms
- Supplementary treatment of IBS
- Start of SF2 treatment (date)
- Prescribed dosage of SF2
- Documentation of gastrointestinal symptoms
Intermediate investigation
- Documentation of gastrointestinal symptoms
- Adjustment of SF2 dosage if needed
- Time of investigation (date)
- Documentation of adverse events
Final investigation at the end of study
- Documentation of gastrointestinal symptoms
- Time of investigation (date)
- Documentation of adverse events
- Global assessment of efficacy by doctor and parentslpatients
- Global assessment of tolerability by doctor and parentslpatients
- Comparative assessment of efficacy of a comparator drug by patientslparents

Table 2: Clinical investigations during the observational study

Patients and methods

Type of study

This is an observational study (Anwendungsbeobachtung, AWB) according to §67-6 of the respective law (Arzneimittelgesetz, AMG) in Germany. The study was conducted according to the "Recommendations for planning and conductance of observational studies" (Empfehlungen zur Planung und Durchführung von Anwendungsbeobachtungen) of the German drug approval authorities (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) as of November 12th, 1998, in accordance with the European guideline E11 of the Committee for Proprietary Medicinal Products (CMPM) of the European Agency for the Evaluation of Medicinal Products (EMEA) (CPMP/ICH/2711/99: Clinical investigation of medicinal products in the pediatric population, December, 2000) and in agreement with the guideline CPMP/EWP/462/95 (Note for guidance on clinical investigation of medicinal products in children, March 17th, 1997).

According to the respective rules, the study did not interfere with medical routine in treatment of childhood abdominal pain but left the management up to the doctor's decision; this included also the dosage and the duration of treatment, and eventually needed supplementary therapy. Doctors were asked to document each patient's data (age, gender, height. weight) and treatment with SF2 during the course of the study. Retrospective inclusion of patients was not permitted. Patients that fulfilled inclusion and exclusion criteria (Table 1 [1]) but were not treated by SF2 were also documented.

The current observational study did not legally require informed consent of patients and their parents, respectively in addition to what is required with every medical intervention, since patients received a therapy based on the doctors sole decision, and no additional risk was involved, data storage and statistical evaluation is allowed in routine praxis as well. Only anonymous data were used for evaluation that did not interfere with legal requirements regarding handling of personalized data and the medical confidentiality rules of the doctor.

According to §67-6 of the AMG, the conductance of the study was registered with the legal representative of private practitioners in Germany (Kassenärztliche Bundesvereinigung), the German drug approval authorities (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and the association of health insurances (Spitzenverbände der Krankenkassen). The study was conducted with an approved medical product. According to AMG, this requires prescription of the drug by a doctor and the usage of regular commercially available products, in addition to individual indication and patient selection.

IBS Type#	N	Age	Gender m:f	height cm	weight kg	duration days*	therapy days+
4 to 11 years							
pain + diarrhrea	25	7.0	8:17	125	27.5	160	41.6
pain + constipation	27	6.4	9:18	124	24.4	108	40.8
pain + alternating	19	7.3	7:12	126	27.1	180	47.5
unspec. pain	36	7.3	17:19	122	26.6	186	40.3
total	107	7.0	41:66	124	26.3	158	42.0
12 to 18 years							
pain + diarrhea	25	14.9	8:17	162	55.7	180	45.9
pain + constipation	29	14.6	3:26	161	56.1	101	52.4
pain + alternating	9	13.7	4:5	157	52.0	464	47.8
unspec. pain	33	14.2	10:23	160	55.4	236	34.2
total	96	14.5	25:71	160	55.4	195	44.0

according to Rome III classification
* duration of complaints (days) until begin of therapy (mean)
+ duration of therapy with SF2 (days) (mean)

Table 3: Sociographic and clinical information

Doctors and patients

This observational study was conducted between October 8th, 2007 (first inclusion) and August 12th, 2008 (last final examination) in 14 general practitioner and pediatric private practices with altogether 203 children in two age ranges, between 4 and 11 years and between 12 and 18 years.

General course of study, duration, dosage

Children age 4 to 18 with IBS that would receive SF2 anyway were to include into the study. It was required to observe the children until significant improvement of symptoms had occurred but for a maximum of 3 months.

SF2 had to be used according to the doctors prescription. The doctor was also asked to document the duration of therapy and the dosage prescribed. The regular dosage in children – as indicated on the patient information sheet – is 1x10 drops/day diluted in water and taken midday, but in adolescents the dosage can be increased up to the adult dosage (30 drops/day).

Because of the non-interfering character of the observational study, neither the type nor the timing of subsequent doctor visits were ruled, and their number and intervals was left up to the individual decision of the treating doctor. However, to be able to estimate the treatment success, it was advised to conduct and intermediate office consultation about 2 weeks after the initial visit, and a final examination after 3 months. The intermediate consultation could also be used to eventually adjust the drug dosage. The investigations to perform at the single visits are listed in Table 2 [2].

Symptom documentation

At any office visit, the presence and severity of the following IBS symptoms were registered: number of stools (per day or per week), stool consistency (hard/lumpy, formed, soft/mushy, liquid, alternating), mucus with stool (yes/no), abdominal pain (yes/no), bloating (yes/no), passing of gas (yes/no), passage of stools (yes/no).

Doctors were also asked to overall estimate the treatment

IBS Type#	N	Pain				Stool frequency stools/day	
		frequent		occasional			
		pre	post	pre	post	pre	post
4 to 11 years							
pain + diarrhrea	25	15	9	2	8	3.32	1.35
pain + constipation	27	11	14	1	5	0.39	0.85
pain + alternating	19	15	4	2	7	1.77	1.17
unspec. pain	36	25	11	2	18	1.48	1.11
total	107	66	38	7	38	1.69	1.11
12 to 18 years							
pain + diarrhea	25	14	11	1	6	3.37	1.18
pain + constipation	29	20	9	1	9	0.38	0.82
pain + alternating	9	7	2	1	3	2.17	1.00
unspec. pain	33	22	11	3	10	1.06	1.02
total	96	63	33	6	28	1.56	1.00

according to Rome III classification

Table 4: Efficacy of SF2 treatment for key IBS symptoms

Symptoms		4 to11 years (n=107)		12 to 18 years (n=96)		Statistics
		pre	post	pre	post	
Bloating	frequent	47	2	40	2	<.0001
Passing gas	frequent	19	0	20	0	<.0001
Mucus in stool	yes	25	0	31	0	---
Imperative urge	yes	53	68*	50	67*	.0002
Straining	yes	50	35	43	25	

* Increase by children that had constipation and had need for straining before

Table 5: Efficacy of SF2 treatment for other IBS symptoms (absolute numbers)

success between "very good" and "poor", and parents and adolescent patients were asked to compare SF2 treatment with previous therapies used and to evaluate SF between "much better" and "much worse". Doctors and parents/patients were also asked to evaluate the overall tolerability and any adverse event between "very good" and "unacceptable".

Statistical evaluation

For the analysis, all documented evaluation sheets were used, and all patients were included (intent-to-treat analysis, ITT). Documented variables are presented with their descriptive values (mean, standard deviation), or as distribution tables in case of qualitative variables. Inference statistics must be regarded as exploratory and non-confirmatory.

Results

Demographics and diagnoses

A total of 203 children and adolescents in two age groups (4 to 11 years and 12 to 18 years) participated in the study and were distributed unequally among the four clinical subtypes of IBS: pain and diarrhea (n=50), pain and constipation (n=56), pain and alternating bowel habits (n=28) and unspecified pain (n=68). All children suffered from IBS according to the Rome III classification (Table 3 [3]).

Table 3 [3] shows the key demographic variables gender, age, height and weight of all patients grouped by age and clinical IBS type. There were no differences noted between the four IBS subtypes with respect to gender, age, and height and weight (age-adjusted).

An IBS diagnosis according to the Rome III classification requires at least 2 months of symptom persistence; accordingly, the doctors participating in this study started treating IBS in the patients after an average 80 days. However, substantial differences occurred depending on the type of IBS symptoms: in general, diarrhea-predominant and constipation-predominant IBS were treated relatively early (median less than 100 days) while IBS alternating and unspecified IBS were started being treated after more than 100 days (Table 3 [3]).

Dosage of SF2, other medication

In 77.4% of cases, patients received the standard children dosage of 1x10 drops per days of SF2, and change of dosing was rare (5% of cases). Only 6 patients received other medication in addition to SF2, and usually for a few days only: 4 x lactulose, 1 x Gastrosil®, 1 x Iberogast®.

Duration of treatment

Mean treatment duration with SF2 ranged between 40 and 50 days in both age groups and all types of IBS (Table 3 [3]), with the exception of "unspecified IBS": these patients were treated an average of 34.2 days. Differences between age groups and IBS types were not significant (p=0.1919).

Efficacy of therapy

Table 4 [4] summarizes the efficacy of SFG2 treatment for the core IBS symptoms abdominal pain and stool frequency (see above) between initial and final examination, broken down by age groups and IBS types. All changes are significant (p<.001).

Also, other IBS associated symptoms such as bloating, passage of gas, mucus in stools and altered stool passage (urge, need for straining) were significantly improved with SF2 (p<.001) (Table 5 [5]).

Global assessment of efficacy

Table 5 [5] also summarizes the global assessment of treatment efficacy by the doctor. In the majority of cases (81.8%) the therapy was judged as "very good" or "good". This is valid for all age groups and all clinical IBS types, with the exception of the IBS alternators age 12 to 18, where doctors evaluated only 55.5% of therapies as "good" or better. However this refers only to a very small number of patients (n=9).

Comparison with previously used medication

Only about 40% patients/parents made respective evaluations thus had experience with other IBS therapies. SF2 was judged as better in 77% of cases, and in only a very few instances, SF2 was regarded as "rather worse" or "much worse" than the comparator drug, with no differences between IBS subtypes and age groups. Previously given drugs were besides diet (1 times), herbal preparations (Iberogast®, 15x), yeast preparations (Parenterol®, 11x) and chemically defined laxatives (lactulose, 10x).

Tolerability, adverse events

Except for two out of 203 cases, patients and parents rated the overall tolerability of SF2 as good or better (98.6%). This is in nearly total agreement with the doctors rating of tolerability: except for two cases 98.5% of treatments were judged as good or better by the treating physician. No adverse events were noted.

Discussion

The irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that is characterized by a typical symptom constellation, i.e. abdominal pain or complaints associated with disturbed defecation. The diagnosis is based of confirmation of this typical symptom pattern, the missing of alarm symptoms (such as fever, weight loss, and blood with stools), and the exclusion of relevant differential diagnoses.

This observational study used the recently published Rome III diagnostic criteria that have been adjusted to childhood functional bowel disorders [3]. It was investigated whether efficacy and tolerability of a probiotic preparation (SF2) can be found under routine conditions in private practice with

children and whether this extends previous studies with the same or similar compounds in adults.

Both physicians a well as parents and (adolescent) patients found the efficacy of the probiotic as good or better in the majority of cases (82% of physicians and 83% of patients) irrespective of the age group and the type of IBS. SF2 was regarded as better than previously used medication (acting on motility or as laxatives) for IBS in all but a few cases.

Therefore, this observational study supplements the increasing number of previously conducted randomized double-blinded and placebo controlled treatment trials in IBS [10] using probiotic preparations that seem to be equivalent or even superior to newly developed chemical compounds for IBS treatment in recent years [14], [15], [16], [17]. This is also confirmed by respective meta-analyses [18], [19], [20], [21].

However, most of these studies have been conducted in adults with IBS. In comparison, only a few studies are available on probiotic treatment of childhood IBS [12], [22], [23].

Henker et al. [12] treated 113 children with acute diarrhea with an E. coli probiotic (Mutaflor®) in a placebo-controlled study and confirmed significant efficacy with respect to response rate, therapy goals and duration to achieve these goals. Bausserman et al. [22] treated 64 children with a lactobacillus GG preparation in comparison to placebo for 6 weeks and found that LGG improved bloating symptoms but not abdominal pain. Gawronska et al. [23] treated 103 children with a similar compound and found moderate therapy efficacy for IBS, but none for pure abdominal pain and functional upper gastrointestinal symptoms. A recent summary [24] of the respective published literature in children concluded that probiotics are not effective in constipation, and a Cochrane meta-analysis summarized that the data base for treatment of childhood IBS is altogether rather insufficient for a final conclusion [25].

Beyond lactobacillus preparations that are confirmed to be effective in adult treatment of IBS [20], [21], other bacterial strains have less frequently been used, and so far only one study has investigated the effects of an inactive E. coli bacterial preparation [26], and another study successfully used a formula of non-living E. coli and Enterococcus feacalis bacteria [14] for therapy of IBS, in addition to the above discussed E. coli treatment of acute childhood diarrhea [12].

The relative homogeneous efficacy of different bacterial strains in the rather heterogeneous gastrointestinal disorder IBS in children and adults [10] calls for an answer to the questions of the underlying mechanism of action of prebiotics and probiotics [26]: It appears unlikely that this will be based on a temporary change of the commensal colonic bacterial flora by new bacterial strains, as was often assumed previously, but instead relies on the stimulation of the innate intestinal immune system through novel bacteria that initiate long-lasting changes in intestinal function. This will have to be studied in the future.

The limitations of the current study are obvious: as this is an observational study, it did not include a control group with either no treatment, or with a placebo treatment. Hence, the data are not controlled for spontaneous variation of symptoms and for a placebo response. Both are, however, known and effective factors contributing to the clinical appearance of symptoms in IBS [27], [28]. Therefore, the efficacy data have to be interpreted with care. A comparison to "treatment as usual" (TAU) in childhood IBS may have allowed to overcome some of the study limitations without randomization into treatment arms as is would have allowed the doctor's decision to be based on clinical criteria only. Finally, while the study applied current diagnostic criteria for childhood IBS, it did not adopt the current standards for efficacy assessment in clinical trials based on "subjective global assessment" (SGA) in IBS, i.e. at least 50% improvement in SGA [29] and therefore may overrate the degree of clinical improvement. Final proof of the efficacy of probiotic treatment in childhood irritable bowel syndromes still requires a double-blinded, randomized and placebo controlled trial.

Notes

Conflicts of interest

The first author (UM) has no conflict of interest, the second author (PE) has a consulting contract with the sponsor (SymbioPharm), the third author (EZ) has performed the statistical evaluation of the study as contract work for the sponsor.

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Optimierung der Versorgungsabläufe in einem interdisziplinären Netzwerk

Marion Matthies

Das KompetenzNetzwerk Orthopädie M-V® ist ein Modellprojekt des Landes Mecklenburg-Vorpommern und wurde in den Masterplan Gesundheitswirtschaft des Landes integriert. Es wurde in Rostock im April 2006 zur Bündelung und Optimierung von Kompetenzen und Synergien ins Leben gerufen. Mitglieder des interdisziplinären Netzwerkes sind die Orthopädische Klinik und Poliklinik des Universitätsklinikums Rostock, die Klinik Ahrensburg, die MTR GmbH und DOT GmbH aus den Bereichen der Medizintechnik, das Orthopädietechnikunternehmen LiEBAU GmbH, die Rehabilitationsklinik „Moorbad Bad Doberan", das Hotel-Neptun als Touristik-Unternehmen und die BioCon Valley-Initiative (Life Science-und Gesundheitswirtschaf tsverbund MV). Die verschieden Netzwerkpartner haben sich zusammengefunden, neue innovative Wege im Bereich der Orthopädie zu bestreiten, gemeinsame Ressourcen zu nutzen, den Ausbau der Kommunikation untereinander und das Marketing zu forcieren, sowie ein

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einheitliches und abgestimmtes Qualitätsmanagement zur Gestaltung der Prozesse zu entwickeln. Dazu haben sie die Organisations-und Managementform des Netzwerkes gewählt. Wirtschaftswissenschaftliche Arbeiten im Bereich des strategischen Managements lassen den Schluss zu, dass zur Funktionstüchtigkeit eines Netzwerkes marktgerechte Wettbewerbsstrategien implementiert und angewendet werden müssen. Jeder Partner erwartet deshalb auch aus dieser Kooperation einen Vorteil für seine eigenen wirtschaftlichen, wissenschaftlichen und politischen Interessen. Aus dieser engen Zusammenarbeit ergab sich bereits eine Vielzahl neuer innovativer Forschungsmöglichkeiten wie z. Bsp. die Entwicklung einer neuen Hüftorthese (FORTHIP-Projekt) oder der neuartigen Revisionspfanne (MARESProjekt). Es konnten bereits Patente angemeldet und eine neue Firma zur Entwicklung von Implantaten gegründet werden. Den Partnern ist es mit seinem Management sehr gut gelungen, ein erfolgreiches und funktionierendes Modell für die Verknüpfung von Wirtschaft, Wissenschaft, Medizin und Tourismus mit Ausbau einer Wertschöpfungskette zur Verbesserung der Versorgung im Bereich der Mobilität/ Bewegung für den Patienten in dieser Region und darüber hinaus zu schaffen. Die Versorgung regionaler, überregionaler und ausländischer Patienten im Rahmen des Netzwerkproduktes „RundumPaket" ist ein Beispiel für die ausgebaute Kooperation der Partner untereinander. Innerhalb jeder Wertkette des Partners finden wiederum eigene Prozessabläufe statt, die durch Schnittstellen mit den Partnern verbunden und optimiert werden. Prof. Mittelmeier Netzwerksprecher und Direktor der Orthopädischen Klinik und Poliklinik des Universitätsklinikums Rostock sagt dazu: „Von der Gelenkprothese bis zum Wellnessurlaub ist alles aufeinander abgestimmt. Der Patient muss fühlen, dass alles wie nach einem Drehbuch läuft". Dem Patienten wird die gesamte Bandbreite der medizinischen Behandlung von der Erstversorgung über die Rehabilitation bis zum Erholungsurlaub über den Netzwerkpfad angeboten. Die Gewinnung neuer Patientengruppen aus dem In-und Ausland unter der Gewährleistung hoher medizinischer Qualitätsstandards, komplexer Serviceangebote für den Patienten und für die mitreisenden Angehörigen werden im Netzwerk gezielt umgesetzt. Zu den Höhepunkten der Initiativen des Netzwerkes zählen außerdem zahlreiche Präsentationen mit Informationsständen und wissenschaftlichen Vorträgen in Deutschland und im Ausland wie z. Bsp. in St. Petersburg, Moskau und Dubai und weiteren Ländern. Perspektivisch wird das Netzwerk weitere interdisziplinäre Fachbereiche (z. Bsp. Radiologie, Chirurgie, niedergelassene Praxen, Logistikund Touristikunternehmen usw.) zur Verbesserung des Servicegedankens für die Gäste und Patienten und der Optimierung der Versorgungsabläufe einbeziehen.

Differences in the haematological profile of healthy 70 year old men and women: normal ranges with confirmatory factor analysis

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Abstract

Background

Reference ranges are available for different blood cell counts. These ranges treat each cell type independently and do not consider possible correlations between cell types.

Methods

Participants were identified from the Community Health Index as survivors of the 1947 Scottish Mental Survey, all born in 1936, who were resident in Lothian (potential n = 3,810) and invited to participate in the study. Those who consented were invited to attend a Clinical Research Facility where, amongst other assessments, blood was taken for full blood count. First we described cell count data and bivariate correlations. Next we performed principal components analysis to identify common factors. Finally we performed confirmatory factor analysis to evaluate suitable models explaining relationships between cell counts in men and women.

Results

We examined blood cell counts in 1027 community-resident people with mean age 69.5 (range 67.6-71.3) years. We determined normal ranges for each cell type using Q-Q plots which showed that these ranges were significantly different between men and women for all cell types except basophils. We identified three principal components explaining around 60% of total variance of cell counts. Varimax rotation indicated that these could be considered as erythropoietic, leukopoietic and thrombopoietic factors. We showed that these factors were distinct for men and women by confirmatory factor analysis: in men neutrophil count was part of a 'thrombopoietic' trait whereas for women it was

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part of a 'leukopoietic' trait.

Conclusions

First, normal ranges for haematological indices should be sex-specific; at present this only pertains to those associated with erythrocytes. Second, differences between individuals across a range of blood cell counts can be explained to a considerable extent by three major components, but these components are not the same in men and women.

Background

The full blood count is one of the most common investigations patients undergo, and has been available since the 1960s. In adults, reference ranges are the same for all ages despite evidence that erythrocyte count and haemoglobin concentration start to decline in men around 40 years of age; age-associated changes in women are less marked [1]. The World Health Organisation defines anaemia as < 13 g Hb/dL for men and < 12 g Hb/dL for women [2], accepting that women generally have lower haemoglobin concentrations than men. It would be logical to conclude that women of menstruating age are likely to be iron-deficient and therefore have lower haemoglobin concentrations, but studies looking at ferritin levels do not support this [3,4], leading to the suggestion that the difference may be due to hormonal influences on red cell production [5]. In the elderly, there is a significant decline in haemoglobin which, as noted above [1], is more pronounced in men than women [6]. This could be due to falling androgen levels in older men. In previous studies, platelet counts have been found to be significantly higher in women [7,8], with possible explanations of compensation for menstrual blood loss or increased thrombopoietin in women being suggested. One study of healthy Caucasian hospital staff found the total leukocyte count to be significantly higher in women than men due to a highly significant difference in neutrophil count, with no significant correlation between monocytes, basophils and gender [9]. The results of a further study, of staff, students and retired academics, confirmed total leukocyte count to be significantly higher in women than men, but did not examine leukocyte differential to determine the cause of this difference [10]. By contrast, a study of 215 men and 272 women aged 62-90 years found that men had significantly higher total leukocyte counts [11]. Laboratory reference ranges for leukocyte counts often do not differ between men and women. Little is known about whether there are any correlations between the different cell counts in healthy adults. The aims of this study were to, 1) identify any correlations between gender and the components of the full blood count in healthy, community-dwelling elderly people, and 2) examine whether there is a statistically-significant relationship amongthe different cell counts, and whether this relationship is gender-specific.

Methods

Sample

Ethics permission for the Lothian Birth Cohort 1936 (LBC1936) study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from Lothian Research Ethics Committee (LREC/2003/2/29). The research was carried out in compliance with the Helsinki Declaration. All subjects gave written, informed consent. Participants were recruited from a potential population of 3,810 people identified from the local Community Health Index as born in 1936 and, as such, might have participated in the Scottish Mental Survey 1947. Full details of recruitment and testing have been published previously [12], but of note is a bias to participation by healthier participants who had relatively higher childhood IQ scores. 1,091 participants attended the Wellcome Trust Clinical Research Facility between 2004-2007 for assessment at mean age 69.5 years (minimum 67.6 years, maximum 71.3 years, 90% of participants aged 68.4-70.7 years).

Measurements

A large number of socio-demographic and health variables were collected at the assessment visit as previously detailed [12]. Blood samples were collected and processed the same day by a LH50 Beckman Coulter instrument. External quality control was provided by UK NEQAS (National External Quality Assessment Service) which includes full blood count each month, and reticulocyte count and differential white cell count every two months. Internal quality control comprised running Coulter 5C single level cell QC and reticulocyte C cell QC first thing each morning. The 5C was repeated at 3.30 pm. Three repeat sample analyses were run at approximately first thing in the morning, lunchtime and early evening. Data were entered into the LBC1936 database and checked [12] with an estimated transcription error rate of 0.13%. Errors

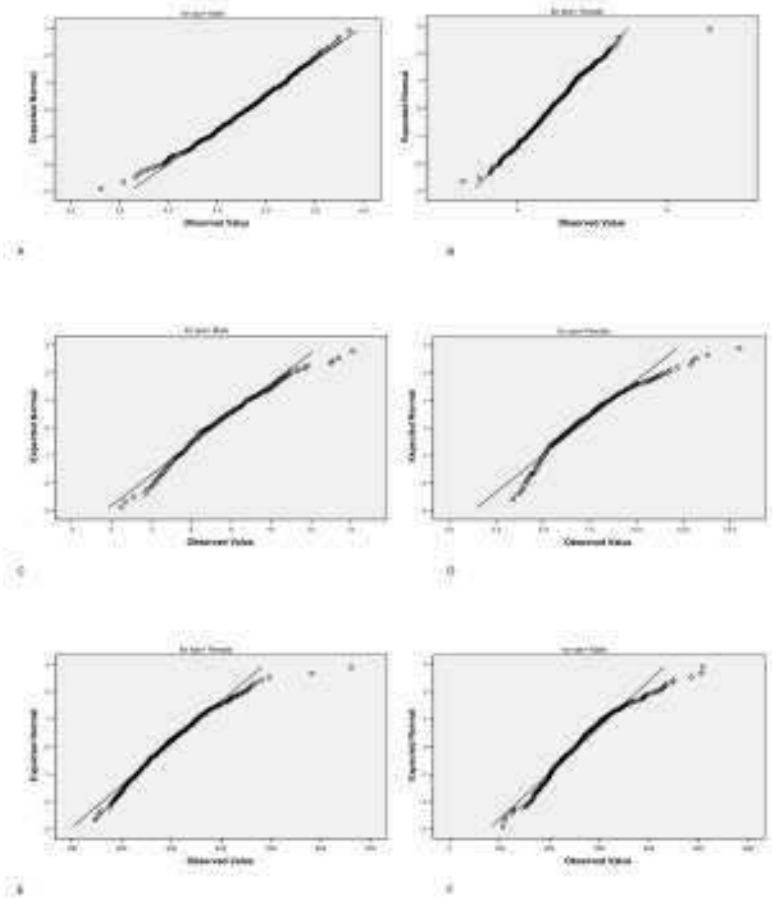

Figure 1. Q-Q plots for blood cell counts by sex. Q-Q plots of cell counts against expected normal distribution for 1027 participants aged 70 years for a) erythrocytes (men), b) erythrocytes (women), c) total leukocytes (men), d) total leukocytes (women), e) platelets (men), f) platelets (women).

Table 1. Blood cell counts by sex

		Red cells	Total white cells	Neutro-phils	Lympho-cytes	Mono-cytes	Eosino-phils	Baso-phils	Platelets
Men	Mean	4.8	7.1	4.6	1.8	0.57	0.18	0.04	257
	Median	4.8	6.9	4.3	1.7	0.54	0.14	0.04	254
	Min	3.3	2.5	1.4	0.5	0.18	0.0	0.01	107
	Max	5.9	14.1	10.9	4.4	1.73	1.15	0.34	507
Women	Mean	4.5	6.8	4.3	1.9	0.48	0.15	0.05	292
	Median	4.4	6.6	4.1	1.8	0.45	0.12	0.04	286
	Min	3.3	3.0	1.6	0.6	0.11	0.0	0.0	131
	Max	6.6	15.5	12.1	4.1	1.38	1.41	0.52	661
	p-value	< .001	.002	< .001	< .001	< .001	< .001	.12	< .001

Blood cell counts in 519 male and 508 female LBC1936 participants at mean age 69.5 years with p-value for difference (Mann-Whitney U test). Red cell count x10^{12}/L, basophils x10^{6}/L, all other cell counts x10^{9}/L.

were mostly small and not systematic. Finally descriptive statistics were run for all numerical data to ensure that all results were within the appropriate scales, and any errors were checked against the original, handwritten datasheets and corrected as necessary.

Statistical analysis

All analyses were performed using the SPSS 16.0 and AMOS statistical packages. We used the Kolmogorov-Smirnov statistic to determine whether variables departed from a normal distribution, noting that the value may be more indicative of goodness-of-fit than the p-value in large sample sizes. We used quantile-quantile (Q-Q) plots fitted to a normal distribution to determine 'normal' ranges for each cell count recognising the inadequacy of defining reference ranges in terms of means and standard deviations [1]. We used Varimax rotation in principal components analyses so as to align components most closely with observed variables facilitating more informative confirmatory factor analyses. Principal components analysis is an exploratory procedure that transforms a number of possibly correlated variables into a smaller number of variables called principal components. Principal components analysis makes no assumptions about how the variables might relate to one another: the number of components that emerge is driven by the data. By contrast, confirmatory factor analysis requires that the researcher specifies a model fully describing the hypothesized relationships between variables. This model is formally tested using structural equation modeling (SEM). Goodness-of-fit indices indicate the fit of the pre-specified model to the data set. Another advantage of SEM is that it can be used to test these assumptions in different samples: here we use this approach to test differences in factor structures between men and women. To determine goodness-of-fit for the structural equation models used for confirmatory factor analysis, we used Chi square at $p < .05$ to accept or reject the null hypothesis that the model provided a poor fit to the data. However, since this might be too conservative for our sample size we also took Root Mean Square Error of Approximation (RMSEA) values < .05 as indicating a good fit, < .08 as indicating an adequate fit and > .1 as indicating a poor fit. We also report the Bentler-Bonnet Index (also known as the Normed Fit Index (NFI)), with values > .95 indicating a good fit and values .90-.95 indicating an adequate fit. For models with more parameters, where the Chi square statistic was significant, we report the Hoelter Index, a measure of sample size adequacy, with values > 200 being acceptable and values < 75 unacceptable.

Results

Descriptive data

One thousand and sixty-two (535 male, 527 female) participants, mean age 69.5 (range 67.6-71.3) years, had full blood count data. Participants were mainly from social classes 1-3 with only 4.1% of participants from social classes 4 and 5 (where a higher number denotes a less professional social class). Ten participants were known to have either leukaemia or lymphoma, one participant thrombocytopaenia, and a further 21 participants reported a diagnosis of anaemia and either current or previous iron, vitamin B12 or folic acid treatment. These participants were excluded from analysis. Two further participants were found to have very raised lymphocyte counts consistent with a diagnosis of chronic lymphocytic leukaemia and were excluded from further analyses. A further two participants had incomplete data leaving a final sample of 1027 participants. Table 1 shows the mean, median, minimum and maximum values by sex for each cell count. All distributions differed significantly from a normal distribution except red cell count in men. There was no significant difference between men and women for basophil counts. Women had significantly higher lymphocyte and platelet counts, though the difference, albeit

Table 2. Normal blood cell count ranges by sex

		Red cells	Total white cells	Neutro-phils	Lympho-cytes	Mono-cytes	Eosino-phils	Baso-phils	Platelets
Men	Min	4.2	5.0	2.8	1.2	0.40	0.10	0.03	210
	Max	5.5	11.1	7.5	2.6	0.80	0.38	0.09	370
Women	Min	3.7	5.0	2.8	1.1	0.35	0.10	0.03	210
	Max	5.4	9.6	6.0	2.9	0.65	0.40	0.11	380

Upper and lower blood cell counts values coinciding with a normal distribution in 519 male and 508 female LBC1936 participants at mean age 69.5 years. Red cell count x10^{12}/L, basophils ×10^{6}/L, all other cell counts ×10^{9}/L.

Table 3. Correlations between blood cell counts by sex

	Red cells	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Platelets
Red cells		.19	-.01 NS	.02 NS	.02 NS	.06 NS	-.03 NS
Neutrophils	.18		.32	.50	.14	.19	.29
Lymphocytes	.02 NS	.05 NS		.59	-.03 NS	-.03 NS	-.02 NS
Monocytes	.11	.39	.28		.15	.15	.17
Eosinophils	.05 NS	.08 NS	.28	.25		.25	.21
Basophils	.03 NS	.22	.16	.22	.25		.26
Platelets	-.02 NS	.28	.05 NS	.16	.13	.21	

Pearson correlation coefficients between blood cell counts in 519 male and 508 female LBC1936 participants. Correlation coefficients for men are in the bottom left section of the Table and those for women in the top right section in bold text. Non-significant (NS) p > .05 marked.

Table 4. Principal components of blood cell counts by sex

	Men			Women		
	1	2	3	1	2	3
Red cells	-.02	-.12	.86	.02	-.02	.97
Neutrophils	.05	.64	.53	.66	.34	.31
Lymphocytes	.77	-.15	.05	.85	-.19	-.08
Monocytes	.53	.32	.42	.87	.17	-.02
Eosinophils	.66	.15	-.04	.01	.66	-.02
Basophils	.46	.47	-.05	.03	.70	.12
Platelets	.01	.81	-.11	.12	.70	-.08

Rotated principal components of blood cell counts in 1027 LBC1936 participants separate analyses by sex.

statistically significant, was small for lymphocyte counts; for all other blood cells men had significantly higher counts (Table 1). Figure 1 shows the Q-Q plots against a normal distribution for erythrocyte, leukocyte and platelet counts by sex. The charts allow the lower and upper values where observed cell count data coincide with a theoretical normal distribution of cell counts to be determined. Table 2 displays the lower and upper limits for each blood cell count by sex. Deviation from a normal distribution is greater in the mid range for blood cells with lower counts such as eosinophils and basophils so that a 'normal' range is more arbitrary. The lower values for all cell types are very similar for both men and women except for red cell count. Inspecting the plots for red cell, total white cell and platelet counts, a clear outlier (not lying on the trajectory of the general curve/line) can be observed for female red cell counts. This outlying participant was excluded from further analyses.

Relationships between blood cell counts: exploratory analyses

Table 3 shows Pearson correlation coefficients between the different blood cell counts by sex; Spearman rho values were very similar (data not reported here). More than half of the correlation coefficients reached significance, with significant correlation coefficients ranging from quite small at 0.11 to quite large at 0.50. Differences between men and women can be examined by comparing across the table diagonal. We did not formally test for significant differences between correlation coefficients in men and women at this stage because of the likelihood of Type 1 statistical errors. Rather, to elucidate relationships between different blood cell counts, principal components were extracted and rotated using a Varimax algorithm. Since the descriptive data indicated that men and women may have distinct processes regulating blood cell counts separate principal components analyses with Varimax rotation were therefore performed for men and women. Both analyses produced three principal components, accounting for a total of 59.5% of total variance in men and 65.5% of total variance in women. Table 4 shows the component matrices. The component structures appear different between men and women. Key differences, looking at values > 0.4, include a stronger positive relationship between neutrophil and lymphocyte counts in women than in men (Component 1), platelet count relates positively to eosinophil and basophil counts in women (Component 2) and men have a stronger positive relationship between red cell, neutrophils and monocyte counts (Component 3). We therefore sought to confirm whether these differences were due to a different structure of relationships between blood cell counts in men and women.

Relationships between blood cell counts: confirmatory analyses

For confirmatory analyses we hypothesised three latent variables corresponding to factor structure that most clearly separated cell counts which occurred in women. We performed structural equation modelling on all seven blood count variables, separately for men and women. We constructed the model so that Factor 1 related to neutrophils, lymphocytes and monocytes, Factor 2 related to eosinophils, basophils and platelets, Factor 3 related to red cells. In women the model fitted with marginal adequacy (RMSEA .074, 90% upper limit 0.80, Hoelter index 226), but fitted poorly in men (RMSEA .14, Hoelter index 68). We then explored the structure in more detail looking at each Component in turn. We excluded participants with anaemia by considering only those who had red cell counts within the normal distribution ranges (as shown in Table 2) in case this was influencing the clear separateness of red cell count. The remainder comprised 473 men and 500 women. First we considered Component 1, hypothesising a latent variable related to lymphocyte, monocyte, eosinophil

and basophil counts as suggested for men in exploratory principal components analysis (Table 4). For men, the model had an adequate fit (Chi-square = 4.24, 2df, p = .12, RMSEA = .049, NFI = .967), whereas for women the model had a poor fit (Chi-square = 31.7, 2df, p < .001, RMSEA = .17, NFI = .893). Next we considered Component 2, hypothesising a latent variable related to neutrophil, basophil and platelet counts as suggested for men in exploratory principal components analysis (Table 4). For men, the model had a marginally adequate fit (Chi-square = 2.60, 1df, p = .11, RMSEA = .058, NFI = .967), whereas for women, the model had a poorer fit (Chi-square = 6.09, 1df, p = .014, RMSEA = .10, NFI = .927). Finally, we considered Component 3. A model with a latent variable related to red cell, neutrophil and monocyte counts, as suggested by Table 4, provided a poor fit for men (Chi-square = 76.9, 1df, p < .001, RMSEA = .11, NFI = .791), and a simpler model comprising red cell and neutrophil counts provided no better fit. Hence, Component 3 was confirmed as essentially identical to red cell count as suggested by the initial principal components analysis for women.

Discussion

In this sample of over 1,000 participants aged about 70 years, significant differences between men and women in full blood count indices were detected. As expected, men had higher red cell counts than women, but they also had higher counts for other blood cell types except for basophils and platelets. For platelets, women had significantly higher counts than men. As Table 2 shows, these differences were not explained by participants whose cell count values fell beyond the normal range, rather, the normal ranges differed between sexes. Moreover, differences between men and women were not restricted to absolute count levels; the relative relationships between different cell types differed between sexes. For both men and women, three principal components emerged. One principal component identified in both men and women was defined by red cell count: this may be usefully considered as an 'erythropoietic' component. This component was also defined to a certain extent by neutrophil count. Another component might be considered as a 'leukopoietic' component which in men was defined by lymphocyte, monocyte, eosinophil and basophil counts, whilst in women, neutrophil, lymphocyte and monocyte counts loaded positively. The final component might be labelled a 'thrombopoietic' component. In men this was described by positive loadings of neutrophil, basophil and platelet counts, whilst in women it relates positively to eosinophil, basophils and platelet counts. Thus the key difference between men and women was found to be the relation between neutrophil counts and other blood cell counts. For men, neutrophil count is part of a 'thrombopoietic' trait whereas for women it is part of a 'leukopoietic' trait. It is important to note that although we have labelled these components as 'poietic', they may relate to processes of blood cell consumption and have nothing to do with bone marrow function or other aspects of cell production. There is a paucity of data on erythrocyte survival in older adults, but it does not appear to differ from young adults or between sexes [13].

Some limited data on the relationship between neutrophils and platelets are available from 34 healthy controls, mostly men, who participated in a study of the effects of type 2 diabetes on leukocyte and platelet counts [14]. Neutrophils, lymphocytes and monocyte counts were all lower in healthy controls than people with diabetes, this being more marked for neutrophils and monocytes than for lymphocytes. By contrast, platelet counts were higher in healthy controls than in people with diabetes. Although the direction of association is opposite in diabetes to that found in our sample, the presence of an association supports the hypothesis that there are underlying factors that drive changes in counts across a range of different blood cell types. Peripherally, one such factor that may link neutrophil and platelet populations is activation by injured atheromatous plaque [15]. Similarly, neutrophil-platelet interactions occur in septic shock [16], suggesting that inflammatory drivers may regulate changes across the haematological profile. There is a paucity of data that inform about these relationships in healthy older adults, but one study investigated nine centenarians, ten older adults (mean age 71 years) and ten younger adults (mean age 35 years) [17]. There were no significant differences between these small groups for erythroid burst-forming units or granulocyte-macrophagic colony-forming units, but centenarians had significantly lower ability to produce interleukin-3. These observations would be consistent with an independent erythropoietic factor. The study did not include data on either eosinophil or megakaryocyte colony forming cells, but alterations in interleukins would be expected to modulate relationships between these cells also if findings from disease states discussed above can be extrapolated to health. In addition to cytokine drivers, alterations in absolute and differential blood counts with ageing may relate to gene expression changes though, again, there is a paucity of data that inform about this [18]. Invoking possible mechanisms is highly speculative at present: further investigation is required into correlates of the different 'poietic' components in healthy adults, especially with regard to sex differences.

Our study has several limitations. First, it examined a narrow age cohort and thus is unable to shed light on possible changes with age. It is possible that haematological profiles and their underlying factor structure may differ in younger versus older populations: age-related changes in both haemoglobin concentration and platelet count are recognised [19,20]. Secondly, the sample was self-selecting as participation was voluntary. Moreover, participants had to be fit enough to travel to the clinical research facility for assessment. These factors introduce a natural sample bias towards more healthy participants; fortunately, we were interested in healthy participants to establish reference ranges rather than unhealthy participants. Thirdly, although our sample was 'healthy' in the conventional terms used for such studies [1,10,11], it included people with a wide range of stable medical conditions. Even though we excluded participants with clear haematological disorders, the mix of these conditions may have influenced the specific components that emerged. Fourthly, in addition to medical conditions, many participants were on regular medication which itself may have affected cell counts, although we were careful to exclude those on haematinics. Further data on healthy populations and at different ages are required to support the results of the present study.

Conclusions

Two principal conclusions can be drawn from the data. First, normal ranges for haematological indices should be sex-specific; at present this only pertains to those associated with erythrocytes. The clinical relevance of different ranges may vary from disease to disease. Second, differences between individuals across a range of blood cell counts can be explained to a considerable extent by three major components, but these components are not the same in men and women. Changes in haematological profile are likely to reflect changes in one or more of these underlying factors.

List of abbreviations

Hb: haemoglobin; IQ: intelligence quotient; LBC1936: Lothian Birth Cohort 1936; NFI: Normed Fit Index; Q-Q: quantile-quantile; RMSEA: Root Mean Square Error of Approximation

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JMS and IJD designed the study. AJG, CEB, JC and MT collected the data. JMS and RMcH analysed the data and drafted the manuscript. All authors contributed to and approved the final manuscript.

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Harnflora Bei Gesunden Frauen

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In den letzten Jahrzehnten zeigen komplikationslose Infektionen der unteren Harnwege (KIUHW) bei Frauen keine Tendenz zur geringerer Verbreitung und Erscheinungsschwere, ungeachtet der Einfachheit der Frühdiagnostik und der Effektivität moderner Antibiotika-Therapie. Bei 80% der Frauen im Alter von 20-40 Jahren beobachtet man KIUHW mindestens einmal im Jahr [1,2,3]. In 70-95% der Fälle wird die Erkrankung auf Enterobakterien, vorwiegend Kolibakterium, normalerweise in Form von Monoinfektionen [4,5,6] zurückgeführt. Auf Empfehlung der European Association of Urology liegt die klinisch signifikante Bakteriurie für die Entwicklung der KIUHW bei $\geq 10^3$ CFU/ml [7]. Dabei hält die Mehrheit der Forscher an der Meinung fest, dass der aszendierende (transurethale) Infizierungsweg der unteren Harnwege, darunter der Harnblase, dominierende Rolle spielt.

Die obigen Bestimmungen sind grundlegend in der Ätiologie, Pathogenese sowie in der moderner Diagnostik der KIUHW. Immerhin erscheint es äusserst wichtig zu sein, die existierenden und möglichen Widersprüche hervorzuheben. Der erste davon – wie hoch ist das methodologische Niveau der mikrobiologischen Untersuchungen? Nach allgemeingültigen und verbreiteten Methode wird die mittlere Harnfraktion auf Standard-Nährböden aufgetragen, zu denen in Russland der Fleischnähragar (FNA), Blutagar und Zuckerbouillon zählen. Jedoch erlauben diese Böden nicht, die zahlreiche Gruppe der nicht-clostriden anaeroben Mikroflora zu entdecken, deren Rolle bei der Entwicklung mehrerer Entzündungsstörungen verschiedener Organe und Systeme längst bewiesen ist [8]. Eine weitere bedeutende Wissenslüke und Widerspruch besteht darin, dass man nicht weiss, ob der Harn einer gesunden Frau steril oder ob er mit transitorischer Mikroflora kontaminiert sei [9]?

Die Aufgabe besteht in der Bestimmung formaler normativen Kennwerte der Anwesenheit der bedingt pathogener Keime im Harn von gesunden Frauen.

Material und Methoden.

Untersucht wurden gesunde Frauen ohne urologische, gynäkologische und sonstige Pathologie in der Anamnese. Im letzten Jahr hatten sie keine Infektionskrankheiten überstanden. Die Gesamt-Blutanalyse und Harnanalyse war unauffällig. Ultraschall-Screening der Harnsystems und innerer Geschlechtsorgane war ohne Befund. Die Frauen wurden in 2 Gruppen eingeteilt, in die I. Gruppe aus 22 Frauen im Alter von 17 bis 24 Jahren, die zuvor kein Geschlechtsleben geführt haben, und in die II. Gruppe aus 24 Frauen im Alter von 18 bis 25 Jahren, die ein normales Geschlechtsleben führen. Durchgeführt wurde 3-fache bakteriologische Untersuchung der mittleren Fraktion des Morgenharns mit Abständen von 3 Tagen. Die Urinaussaat und die Bakteriurie wurden unter Anwendung von Nährböden sowie für aeroben und fakultativ anaeroben Bakterien (Endo, Hichrom candida agar, Hichrom selective enterococcus agar, Eigelb-Salz-Agar, 10% Blutagar, zubereitet auf der Basis des Müller-Hinton-Agars unter Zusatz von Schafserythrozyten), als auch für nicht-clostriden anaeroben (NCA) Bakterien (Müller-Hinton-Nährboden unter Zugabe von Schafserythrozyten, KAB, Blaurock, Schedler Agar und -buillon)bestimmt.DieAussaat-Proben wurde unter aeroben und anaeroben (10% CO_2, 10% H_2, 80% N2) Bedingungen für 2-4 Tagen inkubiert. Die Identifizierung der isolierten Mikroorganismen erfolgte nach morphologischen, tinktorialen, kulturalen und biochemischen Merkmalen mittels Entero-, Neferm-, Staphylo-, Anaerotests (by Lachema, Tschechien). Bei allen isolierten Bakterien wurde die adhesive (AA) und anti-Lysozym Aktivität (ALA) festgestellt (O.V. Bucharin u.a., 1984; V.M. Brilis u.a., 1986) [10,11].

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Ergebnisse.

In keiner von 138 Aussaat-Proben der untersuchten Patientinnen I. und II. Gruppe wurden sterile Harnproben bestimmt. Dreifache Untersuchung für jede Frau in der I. und II. Gruppe liess keine plausiblen Unterschiede in der Artenanzahl und Mikrobenkonzentration in den Harnproben feststellen. Das Mikrobenspektrum im Urin der Frauen aus der I. Gruppe ist in der Tabelle 1 aufgeführt.

Tabelle 1.

Mikroorganismen	Häufigkeit	Durchschnittswert CFU/ml
1	2	3
Fakultativ anaeroben Bakterien:		
Corynebacterium sp.	90,9%	10^2
CNS	90,9%	10^1
Enterococcus sp.	36,4%	10^1
Micrococcus sp.	18,2%	10^2
Staphylococcus aureus	18,2%	10^2
Enterobacteriaceae (Klebsiella sp.)	18,2%	10^1
Streptococcus sp.	9,1%	10^2
Candida sp.	9,1%	10^1
Nicht-clostriden anaeroben Bakterien:		
Propionibacterium sp.	72,7%	103
Peptococcus niger	72,7%	103
Eubacterium sp.	54,5%	104
Peptostreptococcus sp.	45,5%	103
Bacteroides sp.	18,2%	101

Es wurde festgestellt, dass im Urin gesunder nicht sexuell aktiven Frauen Corynebakterien (C.renale) und CNS (S.haemolyticus) dominieren, deren Beteiligung an der

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Entwicklung der KIUHW diskutabel ist. Überraschenderweise wurden zugleich im Harn der Frauen aus der I. Gruppe Mikroben entdeckt, deren ätiologische Rolle bei der Entwicklung der Infektionen von Harnwegen bewiesen ist, nämlich: Enterokokkus, Staphylococcus aureus, Candida, Serratia). Zwar ist ihre Bakteriurie minimal. Neu war auch die Entdeckung von verschiedenen NCA bei Frauen dieser Gruppe, dabei betrug die Keimzahl für einige Arten etwa $\geq 10^3$ CFU/ml (signifikante Bakteriurie für KIUHW). Es sei zu betonen, dass in allen Fällen die Mikroben im Urin im Bestand von aeroben-anaeroben Assoziationen auftraten.

Das Mikrobenspektrum im Urin der Frauen aus der II. Gruppe ist in der Tabelle 2 aufgeführt.

Tabelle 2.

Mikroorganismen	Häufigkeit	Durchschnittswert CFU/ml
1	2	3
Fakultativ anaeroben Bakterien:		
CNS	83,3%	10^1
Corynebacterium sp.	75,0%	10^3
Candida sp.	33,3%	10^2
Bacillus sp.	16,7%	10^2
Staphylococcus aureus	16,7%	10^1
Micrococcus sp.	16,7%	10^1
Escherichia coli	16,7%	10^1
Streptococcus sp.	8,3%	10^1
Enterococcus faecalis	8,3%	10^1
Nicht-clostriden anaeroben Bakterien:		
Peptococcus niger	75,5%	10^2
Propionibacterium sp.	58,3%	10^4
Eubacterium sp.	41,7%	10^5
Peptostreptococcus sp.	41,7%	10^2
Bacteroides sp.	16,7%	10^4
Veillonella sp.	16,7%	10^3
Prevotella sp.	16,7%	10^2
Actinomyces sp.	8,3%	10^1

Der Harn der sexuell aktiven Frauen enthält ein breiteres Artenspektrum von sowie fakultativ anaeroben, als auch NCA Bakterien. Die dominierenden Mikrobenarten bleiben dieselben. In jedem von 6 Fällen kommt Kolibakterie zum Vorschein, die in der I. Gruppe völlig abwesend war. 3,5 mal häufiger kommen Candida Pilze (C.albicans, C.krusei) vor. Unter NCA überwiegen dieselben Peptokokken und Propionibakterien. Jedoch ist die Anzahl der NCA-Keime höher als in der I. Gruppe . Besonders erstaunlich ist die Präsenz eindeutiger Pathogene aus der Gruppe der NCA (Bakteroiden, Prevotella, Aktinomyzeten, Peptokokken, Peptostreptokokken), bekannter Erreger chirurgischer Infektionen, darunter in Weichteilen.

In 92% aller Fälle wurden die Mikroben im Harn im Bestand von aeroben-anaeroben Assoziationen entdeckt und in 8% aller Fälle waren ausschliesslich NCA vertreten.

Bekanntlich wird die Kolonisierung jedes Biotopen durch Symbionten, einschließlich bedingt pathogener Mikroben, durch Ausprägung ihrer Adhäsionsmerkmale entscheidend bestimmt. Gerade dank ihrer Adhäsionsfähigkeit kommt eine ganze Schicht der residenten Mikroben des betroffenen Biotopen zustande.

Bei Frauen aus der I. und II. Gruppe waren 90% der CNS-Stämme adhäsionsaktiv, mit zuverlässiger Erhöhung ($p<0,01$) des Anteils von Maximalwerten in der II Gruppe. In dieser Gruppe war die Zahl der Kulturen mit hoher ALA ebenfalls höher. In allen Fällen waren aus dem Harn isolierten Corynebakterien adhäsionsaktiv. Beachtenswert ist die Tatsache, dass 16,7% von Corynebakterien-Kulturen aus der I. Gruppe keine ALA aufweisen, während alle Corynebakterien aus der II. Gruppe sich durch dieses Merkmal mit überwiegend mittleren und hohen Werten auszeichnen.

S.aureus, isoliert aus dem Urin der Frauen I. Gruppe, zeichnete sich in 50% der Fälle durch hohe AA- sowie ALA-Werte aus. Alle S.aureus Stämme aus der II. Gruppe waren adhäsionsaktiv, ALA war 75% der Kulturen eigen. Bei Enterokokken, isoliert aus dem Urin der Frauen I. Gruppe, war AA in 50% der Fälle und ALA bei allen Stämmen abwesend. Jedoch zeichneten sich alle Enterokokken-Stämme aus der II. Gruppe durch AA und mittlere ALA-Werte aus. Escherichia-Stämme, isoliert aus dem Urin der Frauen II. Gruppe, zeichneten sich in 75% der Fälle durch AA und ALA aus.

Diskussion.

Ungeachtet der grundlegenden Vorstellungen der mikrobiologischen Wissenschaft von der zahlreichen Gruppe der nicht-clostriden anaeroben Mikroflora bei der Entwicklung vieler infektionsbedingter Komplikationen, wird diese Tatsache bei mikrobiologischer Untersuchung des Harns im Normalfall als auch bei der KIUHW insofern nicht berücksichtigt.

Hohe Häufigkeit von aeroben-anaeroben Bakterien im Urin gesunder jungen Frauen widerlegt vollkommen die geltende Vorstellung von der Sterilität des Urins. Den durchgeführten Untersuchungen zufolge können wir von der Keimbesiedlung des Urins durch obligate und fakultative Mikroflora sprechen. Unter den fakultativ anaeroben Bakterien können verschiedene Arten von CNS und Corynebakterien der obligaten Mikroflora zugeordnet werden. Unter NCA gehören Peptokokken, Propionibakterien, Eubakterien und Peptostreptokokken dazu. Nun ist die Notwendigkeit entstanden, den Urin nicht allein nach formal zulässiger Bakteriurie, sondern auch nach dem Spektrum beding pathogener Mikroben, die die Normoflora bilden, zu bewerten. Normale Harnflora setzt sich aus NCA und fakultativ anaeroben Bakterien zusammen, was mit den Vorstellungen von der normalen Mikroflora vieler Biotopen, insbesondere, des Dickdarms und der Vagina, übereinstimmt. NCA, die den grössten Teil der obligaten Mikroflora des Menschen bilden, können bei beliebiger Heransetzung sowie lokaler als auch allgemeiner Infektionsresistenz des Organismus zum Faktor des Infektionsprozesses werden. So wurden von S.M. Funegold, führender Spezialist auf den Gebiet der anaeroben Bakteriologie, etliche Gruppen von Anaeroben isoliert, die bis 75% aller Infektionsprozesse hervorrufen können. Das sind grampositive streng anaerobe Kokken, die der Gruppe Bacteroides fragilis angehören, pigmentierende Arten von Prevotella und Porphipomona, Fusobacterium nuckleatum und C.perfringens» (zitiert nach I.I.Schilnikowa, 2009) [8].

erforschung

Von uns erhaltenen Daten zeugen von geringer Verbreitung und Konzentration von Enterobakterien im Urin junger gesunden Frauen, die den Angaben in der Fachliteratur zufolge, in der äthyologischer Struktur der KIUHW dominieren.

Von unserem Standpunkt aus bildet allein die Erforschung einzelner Arten von Bakterien, die an der Entwicklung der KIUHW mitbeteiligt sind, eine Sackgasse, da sich bei gesunden Frauen im Normalfall aerobe-anaerobe Assoziationen mit komplizierten Inter- und Intrabeziehungen der Arten von Assoziationsmitglieder aus dem Harn isolieren lassen.

Erhaltene Forschungsergebnisse ergeben folgende Schlussfolgerung

1. Im Urin junger gesunden Frauen ist ein breiter Spektrum von aeroben und anaeroben Mikrobenassoziationen enthalten.
2. Im Urin junger Frauen, die das Geschlechtsleben geführt bzw. nicht geführt haben, dominieren immer die gleichen fakultativ anaeroben Bakterien mit relativ niedrigen Konzentrationen (10^1 – 10^2 CFU/ml).
3. Bei grossen Schwankungen der Häufigkeit (16,7-75,5%) verschiedener Arten von nicht-clostriden anaeroben Bakterien im Harn, übersteigt die damit verbundene Bakteriurie meistens (≥ 10^3 CFU/ml) die für den Harn eines gesunden Menschen formal zulässigen Werte.
4. 90% der Stämme von residenten fakultativ anaeroben Bakterien im Urin junger gesunden Frauen zeichnen sich durch ausgeprägte Adhäsionsfähigkeit aus, die meisten Stämme zeichnen sich durch anti-Lysozim Aktivität aus, die von ihrer potentieller Pathogenität zeugen.
5. Weitere Forschungen in mehreren Zentren müssen Untersuchungen uropathogener Eigenschaften von nicht-clostriden anaeroben Bakterien und die Bewertung ihrer klinischen Signifikanz bei der Entwicklung der infektionsbedingten Entzündungsstörungen der Nieren, Harnwege und Geschlechtsorgane zum Ziel haben.

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Noncompaction of ventricular myocardium

Galina Nartsissova, Olga Lenko

Noncompaction of myocardium is genetic cardiomyopathy which is diagnosed by echocardiography. We reviewed 52 cases of noncompaction of myocardium (14 cases of isolated noncompaction, 38 cases of combination of noncompaction of myocardium with congenital heart disease-CHD). Only 18.4% of patients with CHD and signs of noncompaction had myocardial dysfunction with improved after surgical correction. In patients with isolated noncompaction of myocardium was observed clinical manifestations in 42.8%, heart failure with LV dysfunction- in 14.3%. In discussion authors express opinion concerning when this phenomenon is disease or syndrome.

Keywords:

noncompaction of myocardium, genetic cardiomyopathy, echocardiographic criteria, myocardial dysfunction, heart failure.

Noncomaction of myocardium is rare specific form of cardiomyopathy, characterized by presence numerous, excessively expressed trabeculations and deep intertrabecular spases which are informed with a cavity of left ventricle. This phenomenon can be easily diagnosed by echocardiography. The echocardiography and color Doppler are critical importance for diagnosis and family screening of noncompaction of myocardium.

Two forms of left ventricular noncompaction (LVNC) have been described- an isolated form and form associated with congenital heart disease. According to our observations the signs of left ventricular noncompaction in children, especially in infants with congenital heart disease are not rare.

The purpose

of this study was to identify of ventricular dysfunction and the clinical characteristics of patients with congenital heart disease and signs of ventricular noncomaction and patients with isolated noncomaction of myocardium.

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Methods and Results

We reviewed 52 patients with LVNC. The age at presentation was from 4 months to 18 years, prevailed females (57%). From them 38 patients (73%) had associated cardiac lesions-noncompaction of myocardium and congenital heart disease. 14 patients (27%) had isolated left ventricular noncompaction. All underwent clinical examination, electrocardiography, and echocardiography. The 2D-transthoracic echocardiography, 3DEcho was performed using Vivid 7 Dimension (General Electric) with matrix transducers M4S, 5S, 3V. We used the diagnostic echocardiographic criteria of noncompaction proposed by Chin, by Jenni and by Stöllberger.

In patients with LVNC and congenital heart disease the electrocardiogram (ECG) was nonspecific and demonstrated sinus rhythm, ventricular hypertrophy, less often - ST depression in the aVF, V5, V6 (3), right bundle branch block, Wolff-Parkinson-White (WPW) syndrome (1).

The echocardiography showed noncompaction of myocardium at different congenital heart diseases. Prevailed septal defects - 27,7% (10pts), single ventricle -21% (8pts.). Less often it was bicuspid aortic valve (3), aortic valve stenosis (1), coarctation of aorta (1), Ebstein's anomaly (2) and other.

Noncompaction of myocardium was observed by echocardiography in LV lateral wall (95%) and apex. Usually (81,6%) the left ventricular function was normal. However, left ventricular systolic and diastolic function was depressed in 7 patients (18,4%). Left ventricular ejection fraction (EF) in this group was 26 - 52%, the noncompacted layer of myocardium to compacted layer ratio (N/C) -1.5-2.2. They had heart failure in NYHA functional class II.

Noncompacted right ventricular myocardium is very rare because usually RV have many trabeculations. The right ventricle can rarely be affected. In our study noncompaction of myocardium of right ventricle with systolic dysfunction was found out in two patients.

In first case it was total anomalous pulmonary venous connection. Noncompaction of myocardium of lateral wall was found in dilated right ventricle (EDD-3.9cm) with depressed EF (29%). After surgical correction EF of RV increased to 46%. In second case was observed noncompaction of myocardium of inferior segments of lateral wall in hypertrophic RV in patient with pulmonary stenosis, EF - 45%.

In special group are united 10 patients (21%) who had complex cyanotic heart diseases with single-ventricle anatomy. According to our observations often in single ventricle was found noncompaction of myocardium with localization in apex and lateral wall. Ejection fraction was 50-53%, in one case-38%.

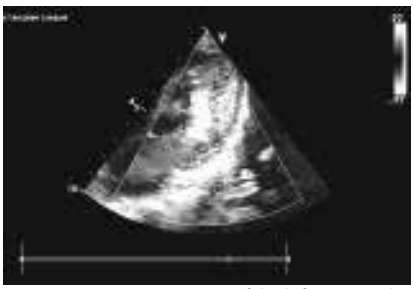

Figure 1. Noncompaction of the left ventricular lateral wall (2D-echocardiography, color Doppler), deep trabecular recess.

We present one rare case of association of LVNC with anomalous left coronary artery from pulmonary artery in boy at the age 13 month. He had heart failure functional class III, LV dilatation (EDV-150ml) and sphericity,

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global hypokinesis, EF -25-28%, mitral regurgitation. 2D echocardiography showed noncompaction of lateral wall, ECG-ST depression and inversion T wave V4-5. Despite adequate surgical correction of CHD the improving of LV function was not.

We examined 14 children with isolated noncompaction of myocardium of left ventricle. With patients had diagnosis: dilated cardiomyopathy (3), arrhythmia (3), foramen ovale (5), mitral valve prolaps, dysplastic heart syndrome (2). Clinical manifestations was observed in 6 patients (42.8%) include heart failure due to LV systolic and diastolic dysfunctions, arrhythmias, intraventricular thrombi located within deep intertrabecular recesses. The left ventricular ejection fraction was 44-67%. The ECG was nonspecific and demonstrated sinus rhythm, tachycardia, ventricular hypertrophy, right bundle branch block, sinoatrial block, WPW syndrome. Two patients (14, 3%), had clinical symptoms of heart failure in NYHA functional class II-III.

Here, we report these two cases of LVNC with heart failure. A 3–year-old girl was observed from 3 month. Echocardiography showed LV dilatation, EF-53-57%, mitral and tricuspid regurgitation, pulmonary hypertension (56 torr). LVNC was located in the lateral wall and the apex. N/C ratio -2.2. (Figure 1.) The left ventricular wall was hypokinetic in these segments. The therapy was not effectively.

The second patient, a 16-year-old boy, had clinical symptoms of heart failure in NYHA functional class III. The

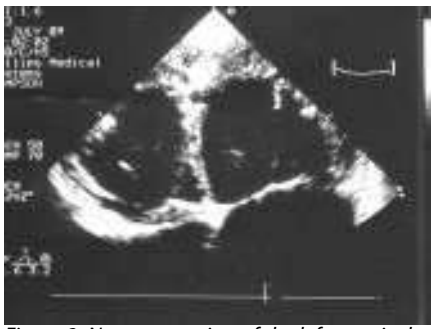

Figure 2. Noncompaction of the left ventricular apex and lateral wall. Thrombus in the left ventricular apex in deep intertrabecular recesses

echocardiography demonstrated all chambers dilatation, LV end-diastolic volume -195ml, spherical index -0.9, EF-21%, global hypo- and akinesis, diastolic dysfunction, mitral and tricuspid regurgitation, pulmonary hypertension.

LVNC localized in apex and lateral wall, N/C ratio -2. Was found the intraventricular thrombi located within deep intertrabecular recesses. One thrombus 1x1 cm was located in apex, smaller - in a lateral wall. (Figure 2). This patient is candidate for the heart transplantation.

We found three family cases of LVNC: two cases in children with CHD and one case at isolated noncompaction.

Discussion

Noncompaction of myocardium is a rare, distinct cardiomyopathy characterized by the presence of numerous, excessive prominent trabeculations and deep intertrabecular recesses which communicate with the left ventricular cavity. The noncompaction of myocardium is included of the World Health Organization in the 2006 in classsification of cardiomyopathies as a genetic cardiomyopathy. There are many studies that showed the genetic basis for left ventricular noncompaction. Various genes have been associated with LVNC. Familial cases account for almost 18% to 50 % of cases in various published series of cases. Frequency of this cardiac anomaly is not yet known; in adults is about 0.05% in population. [3, 4, 9]

LVNC occurs because of a disorder of endomyocardial morphogenesis that results in a failure of trabecular compaction of the developing myocardium. In the early embryonic period human heart consists of spongy meshwork of interwoven muscle fibers and trabeculae. During sixth to eighth week of intrauterine life human heart undergoes compaction of this loose and honeycomb structure. Arrest of compaction results in persistence of trabeculation and deep recesses. [9]

The 2-dimensional and 3-dimensional, contrast-enhanced echocardiography, color Doppler are of critical importance for diagnosis and family screening of noncompaction of the myocardium.

Today are used the diagnostic echocardiographic criteria of noncompaction proposed by Chin et al.(1990), by Jenni et al. (2001) and by Stöllberger et al. The main criteria are such. A two-layer structure, with a thin compacted layer and a thick non-compacted layer measured in end systole at the parasternal short-axis views. LVNC is defined by a ratio of N/C>2, where N- noncompacted layer of myocardium, C-compacted layer of myocardium. [2, 4. 5, 8]

The differential diagnosis for LVNC includes hypertrophic cardiomyopathy with ventricular hypertrophy, dilated cardiomyopathy, left ventricular apical thrombus, and prominent myocardial trabeculations occurring as a normal variant.

LVNC is typically diagnosed for pediatric patients, however the beginning of clinical symptomatic can be delayed during an adult life. Therefore, IVNC may often be undiagnosed. The clinical manifestations include heart failure, arrhythmias and thromboembolism, left ventricular systolic and diastolic dysfunction. [6,9]

In our study includes 38 children with CHD whose we observed noncompaction of myocardium. Given that the process of compacting of myocardium begins on 6-8 week of gestation, when ends the formation of the heart and CHD this indicates on the unity of dysembriogenesis. Arrest of compaction in single ventricle confirms it. Only 18.4% of patients with CHD and signs of noncompaction had myocardial dysfunction with improved after surgical correction. However, at absence clinical symptomatic and LV dysfunctions in 81.6 % of patients, probably we can consider this phenomenon as syndrome. In patients with isolated noncompaction of myocardium we observed clinical manifestations in 42.8%, heart failure with LV dysfunction-in 14.3%.

Early diagnosis of patients may be lifesaving: anticoagulant therapy for patients should be encouraged and screening. The symptomatic patients have a poorer prognosis. The reason – heart failure, ventricular arrhythmias, tromboembolization and sudden cardiac death. The optimal method of treatment is heart transplantation for cases refractory to medical therapy.[1]

Conclusion

Noncompaction of myocardium can affect both ventricles, may be isolated or associated with congenital heart disease. Prognosis in patients with isolated ventricular noncompaction is poor with progression to severe heart failure and death Research is needed to further prognosis in associated ventricular noncompaction with CHD. The patients with noncompaction of myocardium demand observation during a life and preventive maintenance of complications.

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Descriptive epidemiology of screen and non-screen sedentary time in adolescents: a cross sectional study

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Abstract

Background

Much attention has been paid to adolescents' screen time, however very few studies have examined non-screen sedentary time (NSST). This study aimed to (1) describe the magnitude and composition of screen sedentary time (SST) and NSST in Australian adolescents, (2) describe the socio-demographic correlates of SST and NSST, and (3) determine whether screen time is an adequate surrogate for total sedentary behaviour in this population.

Methods

2200 9-16 year old Australians provided detailed use of time data for four days. Non-screen sedentary time (NSST) included time spent participating in activities expected to elicit <3 METs whilst seated or lying down (other than sleeping), excluding screen-based activities (television, playing videogames or using computers). Total sedentary time was the sum of screen time and NSST.

Results

Adolescents spent a mean (SD) of 345 (105) minutes/day in NSST, which constituted 60% of total sedentary time. School activities contributed 42% of NSST, socialising 19%, self-care (mainly eating) 16%, and passive transport 15%. Screen time and NSST showed opposite patterns in relation to key socio-demographic characteristics, including sex, age, weight status, household income, parental education and day type. Because screen time was negatively correlated with NSST (r = -0.58), and exhibited a moderate correlation (r = 0.53) with total sedentary time, screen time was only a moderately effective surrogate for total sedentary time.

Conclusions

To capture a complete picture of young people's sedentary time, studies should endeavour to measure both screen time and NSST.

Background

There has been considerable focus recently on sedentary behavior as a risk factor for negative physical and mental health outcomes in children and adults independent of physical activity [1,2]. Commonly, screen sedentary time (SST) -- and particularly time spent watching television -- is used as a surrogate for sedentary behaviours in general [3,4]. Television is the dominant screen behaviour, constituting about 70% of all SST for children [5,6]. With the high prevalence of overweight and obesity, physical activity guidelines now commonly include SST limits, on the basis that excessive SST may contribute to the problem. A variety of mechanisms linking SST and weight status have been proposed, including the possibility that SST may displace more active pursuits [7], the observation that television time is associated with increased snacking [8], and the fact that television viewing is known to increase exposure to advertisements for high energy density foods [9-11], which has been shown to influence food choices at other times of the day [12]. Sisson and colleagues [13] recently found that nearly half (47%) of US children and adolescents exceeded the recommended two hour daily limit of SST.

From the point of view of researchers wishing to design interventions, SST is an attractive target for several reasons. Increased SST is known to be associated with excessive adiposity in children [6,14], thus reducing SST may help address the issue of childhood overweight and obesity. Screen time is relatively discrete, easily identified, and cheap to measure (in comparison to physical activity which is often measured using relatively expensive instruments such as accelerometers and doubly labeled water). These advantages make it a cost-effective and clear target for surveying, monitoring and parental regulation. Furthermore, SST is seen largely as discretionary time, a "time buffer" which exhibits considerable elasticity to competing demands, and hence is a good target for behavioural interventions.

However, SST is not the only form of sedentary behaviour in adolescents, who also spend substantial amounts of time sitting in school classes, riding in cars, eating, socialising, reading and studying [5]. This non-screen sedentary time (NSST) is relatively under-researched. The underlying assumption in behavioural epidemiology in this area is that SST is a good surrogate for sedentary behaviour in general, that either SST quantitatively dominates sedentary behaviour [15,16], or that patterns of SST (in relation to socio-demographic and health-related characteristics, for example) are similar to patterns of overall sedentary behaviour [17,18]. In adults, Sugiyama and colleagues found that television time was associated with time in other sedentary behaviours in women, but not in men [19]. Amongst UK adolescents, Biddle and colleagues [20] found that television time was negatively associated with other leisure time sedentary behaviours (comprising computer use, sitting and talking, hanging out, listening to music, reading, phone, behavioural hobbies and homework), prompting them to conclude that television viewing did not reflect additional time in other sedentary behaviours. However, it is unclear from Biddle et al.'s (2009) study whether overall SST might be an adequate surrogate for total sedentary time, particularly in light of the exclusion of sedentary activities undertaken at school, on the basis that these activities are not discretionary.

The aims of this study were to (1) describe the magnitude and composition of screen sedentary time and NSST in a random sample of Australian adolescents, (2) describe the socio-demographic, temporal and personal correlates of SST and NSST, and (3) determine whether SST is a suitable surrogate

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for sedentary behaviour in this population.

Methods

Subjects were 2200 randomly selected Australians aged between 9 and 16 years, who took part in the 2007 Australian National Children's Nutrition and Physical Activity Survey (Table 1). The details of the sampling, recruitment strategy and methods of the survey have been reported elsewhere [21]. Briefly, demographic data, including reported annual household income, parental education level, sex and age of the target child were gathered during a computer-assisted face-to-face interview in subjects' homes. Height, body mass and waist girth were measured according to the protocols of the International Society for the Advancement of Kinanthropometry [22], and body mass index (BMI) was calculated.

Table 1. Subject characteristics. Values are shown as percentages or means (SDs).

	Boys	Girls	All
n	1089	1111	2200
Age (years)	13.5 (2.2)	13.4 (2.2)	13.4 (2.2)
BMI (kg.m^{-2})	20.4 (3.9)	21.1 (4.2)	20.7 (4.1)
% obese	5.8	7.1	6.5
% overweight (not including obese)	17.5	20.5	19.0
SEIFA	1004 (66)	1000 (63)	1002 (65)

BMI = Body Mass Index

SEIFA = Socio-economic indicators for areas. SEIFA is a series of indexes of socio-economic status devised by the Australian Bureau of Statistics using a range of indicators such as educational and employment status. The index used here is the Index of Relative Disadvantage, calculated at the postal area level. The national average is 1000 and the SD is 100. Higher values indicate more advantaged areas.

Use of time data were collected using the Multimedia Activity Recall for Children and Adolescents (MARCA) [23]. The software allowed young people to recall everything they did on the previous day from wake-up to bedtime, in time-slices as fine as 5 minutes, using a segmented day format. Young people chose from a list of about 250 activities grouped under seven rubrics (Inactivity, Transport, Sport and Play, School, Self-Care, Chores and Other). The MARCA has a same-day test-retest reliability of r = 0.84-0.92 for major outcome variables [moderate to vigorous physical activity (MVPA), physical activity level (PAL) and SST)], and criterion validity with reference to accelerometry of rho = 0.45 for PAL [23] and rho = 0.54 with reference to pedometry [24]. The MARCA was administered on two occasions. Each time, young people recalled their activities over the two previous days (i.e. a total of four days were sampled). Wherever possible, at least one school day and one non-school day were sampled.

Data treatment

NSST was calculated as the number of minutes the adolescent reported being involved in activities when seated or lying down expected to elicit <3 METs, as listed in the MARCA compendium [25] with the exception of sleep. While some have suggested that sedentary time may be defined on the basis of energy expenditure as 1.0-1.5 METs (with 1.6-2.9 METs classified as light activity) [26], for the purpose of this paper we defined sedentariness in terms of activity type, based on the meaning of the original Latin term sedere ('to sit') [27]. We felt it was important to include all sitting activities <3 METs since inactivity physiology research has found differences in cellular mechanisms, such as electromyogram patterns, across sitting, standing and locomotive activities [2]. However, it is noteworthy that the seated activities with an energy expenditure >1.5 and <3.0 METs, such as sitting and talking, contributed only 2.2% of total NSST minutes. Seated activities which were excluded from NSST based on energy expenditures >3 METs included playing drums (4.0 METs) or trombone (3.5), horseback riding (4.0) and cycling (4.7).

Screen time was the number of minutes the adolescent reported watching television, playing videogames or using a computer. Total sedentary time was calculated as the sum of SST and NSST, although it should be noted that this time is not strictly speaking sedentary (that is, performed while seated), since adolescents often watch television, eat, read, study and otherwise conduct their lives lying down. Some seated activities exceeded the 3 MET limit and thus were excluded. Since Australian children spend about one day in two at school, overall SST, NSST and total sedentary time were calculated as the average of school day and non-school day values.

Reported household income was stratified into four bands: >AUD104,000; AUD75,000-104,000; AUD52,000-75,000; and <AUD52,000, based on Australian Bureau of Statistics classifications. Education level was based on the highest level reported by either caregiver, and categorised as high school only, some post-secondary education (e.g. trade certificate or diploma), or university degree. Remoteness of residence was stratified into four bands using the Accessibility/Remoteness Index for Australia ("ARIA+") method [28]: major city, inner regional, outer regional and remote.

Weight status category (thin, normal weight, overweight or obese) was calculated using the criteria of Cole et al. [29].

Statistical analysis

The magnitudes of SST, NSST and total sedentary time were described as means and standard deviations. The relationships between socio-demographic characteristics and SST, NSST and total sedentary time were determined using one-way ANOVA (for categorical variables) or regression (continuous variables). To examine whether SST was an adequate surrogate for total sedentary time, Pearson's r was used to quantify the strength of the relationship between SST and total sedentary time. Further analysis using linear regression (for continuous independent variables) and ANOVA (for categorical independent variables) tested whether the residuals were significantly associated with other socio-demographic or use of time variables. High and low SST categories, and high and low total sedentary time categories were created using median splits, and cross-tabulation was used to calculate the degree to which adolescents with high total sedentary time could be identified using SST as an index. Except for when comparisons were made across sexes and ages, values for SST, NSST and total sedentary time were adjusted for age and sex by regressing them against decimal age and fitting a fourth-order polynomial. This was done separately for boys and girls, and the residuals were used in analysis where appropriate. Paired t-tests were used to compare SST, NSST and total sedentary time on school vs. non-school days. Alpha was set at 0.05. No corrections were made for multiple comparisons, but exact p-values have been reported.

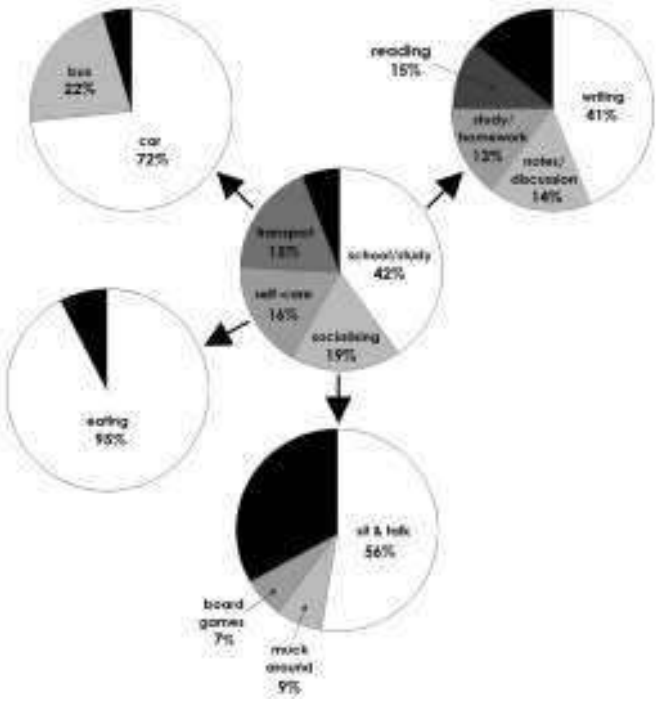

Figure 1. The components of non-screen sedentary time (NSST). The central circle represents all NSST divided into the major domains, and the peripheral circles the contributors within each domain. The unlabeled black areas represent the total of minor contributors within each domain.

Results

The magnitude of non-screen, screen and total sedentary time

Adolescents spent 345 ± 105 minutes/day (mean ± SD) in NSST, 230 ± 114 minutes/day in SST, and thus 575 ± 101 minutes/day in sedentary activities in total. Overall, NSST constituted 60% of total sedentary time. The average duration of a bout of NSST was 28.5 minutes. The longest reported bouts of continuous sitting were for social talking (e.g. at parties and get-togethers, 123 minutes), part-time work (105 minutes), cinema (100 minutes), knitting and sewing (63 minutes) and watching live sporting events (62 minutes).

More than one-third (42%) of NSST consisted of school-based or study activities. Of this, 41% was spent writing, 15% reading, 14% taking notes or class discussion, and 13% study or homework. The next biggest contributors were social activities (19% of NSST), of which sitting and talking constituted the largest part (56%), followed by "mucking around" (non-specific seated activity; 9%) and board and card games (7%). Self-care constituted 16% of all NSST, to which the overwhelmingly greatest contributor was eating (95%). Passive transport, mainly by car (72%), constituted 15% of NSST (Figure 1).

The relationship between non-screen, screen and total sedentary time and socio-demographic and personal variables

Table 2 shows SST, NSST and total sedentary time across various socio-demographic categories and day types. These relationships are summarised visually in Figure 2. In general, SST and NSST showed opposite socio-demographic gradients.

Age and sex

There were significant age-related differences in NSST ($p < 0.0001$). NSST decreased until the peri-pubertal years (12-14) and then increased again among older adolescents (Figure 2). The inverse pattern was seen for SST, which peaked in the peri-pubertal years. Total sedentary time rose linearly across the age bands at the rate of about 9 minutes/day per year of age, from 541 (93) minutes/day at age 9 to 603 (114) minutes/day at 16.

Boys accrued 33 fewer minutes/day of NSST than girls ($p < 0.0001$) when adjusted for age, however they accumulated considerably more SST (50 minutes/day more; $p < 0.0001$), and hence more total sedentary time (by 18 minutes/day; $p < 0.0001$).

Day type

NSST was 155 minutes greater on school days than on non-school days (425 ± 102 minutes/day versus 270 ± 125 minutes/day; $p < 0.0001$), whereas SST was 93 minutes lower on school days ($p < 0.0001$). Consequently, total sedentary time was 62 minutes/day greater on school days than on non-school days ($p < 0.0001$).

Household income and parental education

When adjusted for age and sex, adolescents from the highest income households experienced the highest levels of NSST, accruing 29-39 minutes/day more than adolescents from other income bands ($p < 0.0001$). In contrast, SST was highest in the poorest households ($p < 0.0001$). Total sedentary time was not significantly different across income bands ($p = 0.52$), varying by no more than 7 minutes/day across income bands. Similar patterns were seen for parental education. Adolescents with at least one university-educated parent accumulated 37-46 minutes day more NSST than adolescents with parents of lower educational levels ($p < 0.0001$). Conversely, SST was highest among children of high-school educated parents (251 minutes/day), and lowest among children of university-educated parents (215 minutes/day; $p < 0.0001$). There was a weak but significant ($p = 0.0015$) association between education level and total sedentary time, although the differences amounted to no more than 17 minutes/day.

Geographical remoteness

NSST was significantly associated with geographical remoteness ($p = 0.0015$). Adolescents living in major cities accrued more NSST (351 minutes/day) than adolescents living in inner regional (335 minutes/day) or remote (321 minutes/day) areas. Screen time did not differ significantly across geographical areas, however total sedentary time did (adolescents in major cities experienced 46 minutes/day more than remote adolescents; $p < 0.0001$).

Weight status

NSST was associated with weight status ($p = 0.003$), with leaner adolescents generally accumulating more NSST. Normal weight adolescents experienced 25 minutes/day more NSST than obese adolescents. BMI z-score was significantly ($p = 0.005$), but weakly and negatively ($r = -0.06$), associated with NSST, as was age- and sex-adjusted waist: height ratio ($r = -0.05$, $p = 0.02$).

Screen time showed the opposite gradients, being higher in obese adolescents (274 minutes/day) than in overweight (240 minutes/day) and normal weight adolescents (224 minutes/day; $p < 0.0001$). Total sedentary time also increased as weight status increased, from 573 minutes/day

Table 2. Adjusted mean (standard deviation) values (minutes/day) for non-screen sedentary time (NSST), screen time and total sedentary time (TST) across selected socio-demographic categories.

		NSST	Screen time	TST
All adolescents		345 (105)	230 (114)	575 (101)
Sex [2]	Boys	328 (104)	255 (117)	584 (104)
	Girls	361 (102)	205 (103)	566 (94)
		p < 0.0001	p < 0.0001	p < 0.0001
Day type	School days	425 (102)	181 (102)	606 (102)
	Non-school days	270 (125)	274 (151)	544 (128)
		p < 0.0001	p < 0.0001	p < 0.0001
Household income [1]	1st band (wealthiest)	370 (101)abc	204 (98)abc	578 (97)
	2nd band	341 (98)a	232 (110)ade	573 (99)
	3rd band	337 (100)b	234 (110)bd	571 (105)
	4th band (poorest)	331 (104)c	248 (117)ce	578 (98)
		p < 0.0001	p < 0.0001	p = 0.52
Parents' education [1]	University	369 (104)ab	215 (105)a	584 (102)a
	Some post-secondary	332 (96)a	236 (111)a	567 (103)a
	High school only	323 (105)b	251 (114)a	573 (93)
		p < 0.0001	p < 0.0001	p = 0.0015
Remoteness [1]	Major city	351 (97)ab	234 (103)	586 (95)abc
	Inner regional	335 (104)a	229 (114)	564 (98)ad
	Outer regional	344 (105)c	220 (104)	565 (101)be
	Remote	321 (95)bc	219 (115)	540 (104)cde
		p = 0.0015	p = 0.12	p < 0.0001
Weight status [1]	Obese	324 (105)ab	274 (124)abc	598 (110)ab
	Overweight	335 (95)cd	240 (100)ad	574 (100)a
	Normal weight	349 (104)ac	224 (110)bd	573 (97)b
	Thin	357 (110)bd	222 (111)c	579 (101)
		p = 0.003	p < 0.0001	p = 0.03

Values in the same section and row with the same superscript are significantly different (p < 0.05). For NSST across household income bands, for example, the wealthiest band is significantly different form all other bands.
[1]Adjusted for age and sex
[2]Adjusted for age

for normal weight adolescents to 598 minutes/day for obese adolescents (p = 0.03).

Screen time vs. television time

Television time constituted about 70% of SST, and was strongly correlated with SST (r = 0.73, p < 0.0001). However, the correlations were less strong for boys (r = 0.66) than for girls (r = 0.83), and for older adolescents (r = 0.67-0.70 for 14-16 year olds, r = 0.79-0.84 for 9-13 year olds). These differences reflect differences in videogame time in boys, and computer time in older adolescents. The socio-demographic patterns which characterised SST also characterised television time. Boys experienced 10 minutes/day more television time than girls (p = 0.005), and in both sexes television time peaked at ages 12-13 years. Television time was 65 minutes greater on non-school days than on school days (p < 0.0001). Television time was inversely related to educational status and income (both p < 0.0001; adolescents from households in the wealthiest quartile accumulated 30 minutes/day less television time than adolescents from the poorest quartile). Television time increased with weight status (p < 0.0001), with obese adolescents experiencing 37 minutes more television time each day than children of normal weight.

Is screen time an adequate surrogate for total sedentary time?

In spite of a significant negative correlation (r = -0.58, p < 0.0001) between SST and NSST, there was a moderate linear relationship between SST and total sedentary time (r = 0.53, p < 0.0001), which was relatively consistent across genders (r = 0.57 for boys, r = 0.47 for girls), but decreased slightly across age groups (from r = 0.65 for 9 year olds to r = 0.44 for 16 year olds). The residuals of the SST -total sedentary time regression were not significantly related to sex, BMI z-score or weight status category, but were related to age (p < 0.0001; older adolescents showed larger residuals); area-level SEIFA (p = 0.008; higher SES areas showed larger residuals); household income (p < 0.0001; wealthiest quartile had larger residuals); and parental education (p < 0.0001; higher parental education associated with larger residuals). Therefore, the usefulness of SST as a surrogate for total sedentary time was reduced in older adolescents of higher socio-economic status. Identifying adolescents as being in the high or low total sedentary time category (using a median split) based on their having high or low SST correctly classified them in 66% of cases (69% for boys, 64% for girls). Classificatory success decreased across age groups from 70% for 9 year olds to 61% for 16 year olds,

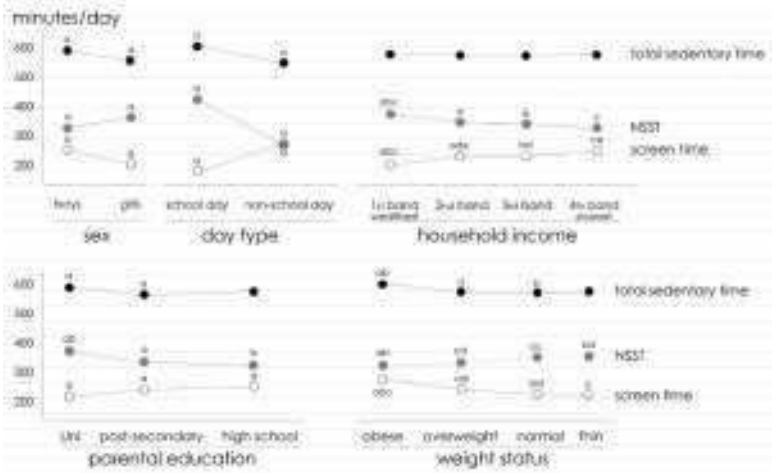

Figure 2. Relationships between socio-demographic variables and total sedentary time (black dots), non-screen sedentary time (NSST; grey dots) and screen time (white dots). Datapoints joined by the same line with the same superscript are significantly different from each other. Uni = university.

and across age groups (79-85% across each age from 9 to 16 years). Therefore, SST proved to be only a moderately effective predictor of total sedentary time.

Discussion

Screen time and NSST showed opposing patterns in relation to key socio-demographic factors, such as sex, age, weight status, household income, parental education and day type. The contrasting patterns of NSST tended to compensate (at least partially) for SST across socio-demographic groups. One interpretation of this compensatory effect may be that adolescents have a homeostatic mechanism regulating sitting time, a "sedostat" analogous to the "activitystat" hypothesis proposed by Wilkin et al. [30]. Wilkin and colleagues [30] have suggested that increasing physical activity in one domain (e.g. school) may result in decreasing physical activity in another (at home). Similarly, it may be that reduction of SST will result in increased NSST. This hypothesis has synergies with the 'compensation effect' described by Biddle et al. [5] where adolescents switch between sedentary choices rather than accruing additional total sedentary time. Another possible explanation relates to behavioural economics theory, which suggests adolescents often make choices between being physically active or sedentary and are influenced by both reinforcing and constraining environmental and social factors. If such a homeostatic mechanism exists, it is unclear whether it has a physiological, environmental or social basis, or a combination of such influences [31].

Regardless, SST and NSST should not be seen as qualitatively equivalent or interchangeable. The energetic demand of SST (mean = 1.3 METs) is estimated to be somewhat lower than NSST (mean = 1.5 METs). Additionally, NSST is often considered to be more socially "valuable" than SST. From a use of time point of view, SST is much more "permeable" than NSST, that is, it allows for fragmentation (interspersing bouts of SST with other activities) and time compression (reducing total time commitment by multi-tasking). Furthermore, television time is associated with exposure to food advertising and with increased snacking, and hence perhaps with unfavourable dietary habits [8]. In contrast, time spent in sedentary homework activities has been associated with more favourable dietary habits, such as increased fruit and vegetable intake [32]. Because of these numerous differences, reducing NSST is unlikely to be functionally equivalent to reducing SST in terms of modifying energy balance.

An important question is the extent to which SST can be used as a surrogate for, or a predictor of, total sedentary time, given that SST is the most commonly measured aspect of total sedentary time. The correlation between SST and total sedentary time was moderate (r = 0.53) but highly significant. However, the standard error of estimate (86 minutes/day) was large, suggesting that in 95% of cases total sedentary time could only be predicted from SST to within about 172 minutes/day, or about 30% of mean total sedentary time. Using median splits, SST could only be used to correctly categorise adolescents into high or low total sedentary time in about two thirds of cases. The predictive power of SST varied with age, parental education, household income, and area-level SES, suggesting that it may be less useful in predicting total sedentary time in particular groups, particularly older adolescents from high SES families.

The specific strengths of this study include the large sample size, the random nature of the selection process, the wide age range, and the fact that activity was assessed using a methodology which yielded very high-resolution use-of-time data. This is also the first study to comprehensively describe NSST, and to compare it to SST. The study nonetheless has limitations. The use of time approach did not capture multi-tasking, asking adolescents to nominate the activity they were most focused on, or dividing stretches of time between two activities. The survey was conducted mainly in autumn and winter, and seasonal patterns may affect both SST and NSST. There are also well known limitations to self-report, particularly with younger children, although the instrument used has been shown to have high reliability and good validity. In this study, however, the self-reported duration of daily TST (575 minutes/day) was somewhat larger than objectively measured TST reported in young people of similar ages; i.e. ~364-450 minutes per day [33-35]. This may be because accelerometers are typically not worn throughout the entire waking day (about 15 hours in this sample). Accelerometer data are often included in analyses if the participant provides >8 h of valid recording per day. Accelerometers may be removed prior to bed and not capture time spent lying awake in bed and other sedentary aspects of the pre-bedtime routine. The choice of accelerometer cut-point used to define sedentary behaviour is also likely to influence the measurement of TST.

Conclusions

There has been great concern over secular increases in fatness in children and adolescents. Many interventions are predicated on increasing physical activity and/or reducing sedentary behaviour as a means of improving energy balance [36,37]. Some studies have been successful in improving weight status by focusing on reducing SST [38]. Despite the inverse relationship between weight status and NSST identified in this study, scope remains for interventions targeting NSST, such as active lesson breaks in the classroom [39], or active transport to school [40].

While television time appeared to be a passable surrogate for overall SST, SST was only a moderately effective predictor of total sedentary time. Furthermore, the relationships between SST, television time and total sedentary time vary within certain subsets of the adolescent population or on certain day

types. Therefore, future surveys should, as much as possible, attempt to capture NSST as well as SST for a more complete picture of sedentary behaviours in adolescents.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

This study involved secondary analysis of an existing large dataset. All authors participated in the conception of the study and drafting the manuscript. TO and DK carried out the statistical analysis. TO oversaw collection of the original dataset. CM coordinated drafting of the manuscript. All authors read and approved the final manuscript.

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New method of conservative treatment of cervical disc herniations

Andrey Oleynikov, Andrey Remnev

Cervical disc herniations are a very serious clinical question. The hernia of cervical disc is very widespread problem which arises at various pathological conditions. More often this pathology is complication (or result of development) degenerate changes cervical intervertebral disks. Treatment of this serious pathology can be operative or conservative. Cervical radiculopathy is basic clinical display cervical disc herniations.

Principal causes of it consist in a mechanical compression of spinal backs, their resulting or taking away vessels, and also cervical department of a spinal cord and vascular textures. Treatment of cervical disc herniations presents known difficulties and can be operative and conservative. We are engaged in conservative treatment of a pathology of a backbone various genesis, including, cervical disc herniations. In the course of this work we have developed a new way of treatment of this pathology. In 2011 we have received the positive decision on delivery of the patent for the invention of the Russian Federation on this method.

The essence of this invention consists that in a combination to hypodermic introduction of a mix of ozone and oxygen of 50 Hz, a current strength 5-7 mA, duration of an electric impulse 0,3 ms (with a solution Papain or Karipain), duration of procedure of 10-14 minutes every other day, on course of treatment of 7-10 procedures carry out electric stimulation of a place of introduction of this mix of gases by a pulse electric current by frequency. Originally we do by the patient test on ozone introduction. Treatment should be carried out only at negative result of this test. This method is directed on reduction and knocking over of a painful syndrome at patients with cervical disc herniations.

Throughout 2008-2010 under our supervision there were 417 patients with cervical disc herniations at the age from 23 till 58 years. The spent treatment has allowed to achieve reduction and disappearance of a painful syndrome from all patients. We observed improvement, and in most cases — restoration radicular nervous carrying out. The spent treatment by new way hasn't revealed cases of deterioration of a condition sick, both clinical, and functional or morphological.

Thus, application of a new way of treatment allows to eliminate a painful syndrome, to restore radicular nervous carrying out at patients with cervical disc herniations.

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Efficiency of the multi-field medico-surgial private clinic

Viktor Paramonov; Alexander Davydov; Vladimir Dolishniy

Doctor Paramonov's clinic (located in Saratov, Russian Federation) has been an active member of the European Academy of Natural Sciences since 2008; it is one of the first multi-field medico-surgical private clinics in Russia. It started its activities in 2007.

The general director of the clinic is Paramonov Viktor Alexandrovich, the famous cancer surgeon with more than thirty years of work experience, professor, doctor of higher category, the author of the unique surgery methods for head and neck tumor.

The specialists working in the clinic have higher and first qualifying categories, the degrees of Candidates and Doctors of Medicine. They provide inpatient and outpatient medical services in more than sixty clinical specialities, such as oncology, surgery, obstetrics and gynecology, proctology, otolaryngology, urinology, traumatology and orthopedics, neurosurgery, thoracic surgery, vascular surgery, neurology, gastroenterology, therapy, endocrinology, hepatology, rheumatology, surgical cosmetology, pulmonology, rheumatology, allergology and immunology, massage, chiropractic, psychotherapy, etc.

Equipment of the clinic currently satisfies the requirements of the European standards: there are the departments of ultrasound examination and endoscopic diagnosis, the department of CT and X-ray, the laboratories of clinical, biochemical, cytological and immunological research. There is the successfully operating Centre of Clinical Hemostaseology in the clinic which is equipped with all modern facilities. The Center of Human Reproduction which includes all the fertility treatments is working at the clinic since March, 2009. According to incomplete statistics, during the work of the Center about 3500 long-awaited children were born. The effectiveness of IVF programs in the Center of Reproduction is about 48%.

The clinic consists of two departments: outpatient and inpatient with 20 beds. The main characteristics of the functioning of the outpatient clinic are shown in Table 1.

Table 1. Characteristics of the functioning of the outpatient clinic

Year	2007	2008	2009	2010
The total number of outpatient visits	20292	44022	67003	83303

Annually, the clinic performs about 1500 surgeries. Every tenth resident of Saratov received medical care in the clinic in 2010.

Doctor Paramonov's Clinic provides day inpatient stay and day-and-night station. The patients may choose highly comfortable one- or double- rooms.

Table 2. The main characteristics of the inpatient clinic

Year	2007	2008	2009	2010
The number of surgeries	1978	2309	3073	3159
The average number of operations carried out on a bed	98,9	115,5	153,7	157,9
The average inpatient stay	3,28	3,.3	3	2,82

The clinic has performed more than 10% of all surgeries in Saratov.

Prof. Viktor Paramonov
oncology surgeon, general director of clinic

Prof. Vladimir Dolishniy
surgeon of the higher category

Table 3 presents the main types of surgeries performed in the clinic.

Table 3. Characteristics of types of surgeries preformed in the clinic

Year	2007	2008	2009	2010
Surgery (abdominal and thoracic)	507	550	574	627
Head and Neck Surgery	326	310	323	377
Gynecology	775	825	1406	1394
Neurosurgery	10	34	58	41
Otorhinolaryngology	244	413	501	493
Vascular Surgery	20	20	15	47
Urology	65	123	117	102
Traumatology and Orthopedics	31	29	69	78
Total	1978	2309	3073	3159

According to the quality assessment of the medical services performed by the Department of Statistics and expertise "Rosfinprom", Doctor Paramonov's Clinic is awarded the diploma "The best medical institutions of the Russian Federation" and was entered into the National Register of "Leading healthcare institutions of Russia". In 2009 two specialist of the clinic – general director V. Paramonov and the head of the Center of the Human Reproduction O.V. Kruttsova were awarded diplomas in the nomination "Best Doctor" of the directory "100 best medical institutions of the Russian Federation in 2009".

The clinic is constantly involved in charitable work: its specialists regularly provide free consultations for the retired, it participates in the interregional public organization "Golos", provides financial assistance to churches, children's and youth sports clubs in Saratov and the region.

Thus, the clinic makes a significant contribution to the public health service in Saratov and Saratov region.

Private Surgical Clinic JSC Clinic doctor Paramonova, Saratov, Russia

Preventive and rehabilitation measures for youth suffering from vegetative-vascular dystonia

Viktor G. Pashchenko

Urgency of the Issue:

Nowadays vegetative-vascular dystonia is the most widespread pathematoloy of student youth special medical groupes (according to Luhansk students' case rate research: Luhansk Taras Shevchenko National University - 580 students suffering from vegetative-vascular dystonia, V.G. Pashchenko; Medical University - 430 students suffering from vegetative-vascular dystonia, V. Siroshtan; East Ukraine Volodymyr Dahl National University - 720 students suffering from vegetative-vascular dystonia, V.P. Liapin). This is arised from original disposition and influence of factors variety, one of these factors is psychic tension. Pathematoloy process has a tendency to quickening. It is featured with plenty of human offenses, which decrease a lot "life quality", physical and social adaptation. Over recent years WHO (World Health Organization) Committee emphasized continually the importance of cardiovascular diseases prevention starting with the childhood, which is often the beginning of hypertensive disease, atherosclerosis and ischemic heart disease.

Annotation:

Preventive and Rehabilitation Measures for Youth Suffering from Vegetative-vascular Dystonia by physical exercise implementation. It is different because of adding therapeutic swimming to physical exercises. Swimming charge is more than 5 km 200 m in the swimming pool for 20 weeks. And is accompagnied with boat-type medical trainer with the charge 1811600 kg/m for 44-45 days and 20 times of positive psychological impact. Method by p. 1, which is different because of conduction of boating with the charge 1811 600 kg/m for 44-45 days within 908 minutes and 1860 paddles.

Method by p.l, which is different because of conduction of 20 times of positive psychological impact, which is strengthened with music underneath.

Method by p.l, which is different because of filling the room of psychological impact with plants, having sedative and good for vessels influence, essential oil volatile fractions. Method by p.l, which is different because of filling the room of boating with negative ions within the concentration of 500-5000 ions/sm and relative moisture 30-40%. In the Scientific and Research Department V.G. Pashchenko has invented "Preventive and Rehabilitation Measures for Youth Suffering from Vegetative-vascular Dystonia". Patent of Ukraine N° 33332 from the year 2008.

These Preventive and Rehabilitation Measures are comfortable and economic, can be used across-the-board. This is extremely important for people general psychosomatic health improvement.

Prof. Viktor G. Paschenko

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Upper gastrointestinal mucosal coat state in cholelithiasis patients after laparoscopic cholecystectomy and following rehabilitation treatment course

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According to data provided by a number of foreign and local researchers, gallstone disease is one of the most common hepatobiliary system disorders, which has been displaying a constantly increasing trend within the last 10 years. Gallstone disease indicants are observed in one fourth of the planet's population in the age of over 60, and in one third in the age of over 70. Gallstone disease morbidity rate in Ukraine has increased by 44.6% within the last several years, coming up to 93.4 cases per 100.000 inhabitants.

The growth of gallstone disease morbidity rate leads to a considerable increase of cholecystectomies. However, surgical removal of gallbladder does not always solve cholelithiasis-related issues. Since gallbladder performs a number of functions, such as storage, concentrative, evacuative, bibulous, secretory, humoral etc., which ensure sphincteric apparatus of biliopatreatoduodenal zone synchronic operation, the deprivation of this functional organ and its physiological role requires adaptation of the body to new conditions, associated with the exclusion of bile from digestive process and liver exocrine function changes. Incoordination of sphincteric apparatus operation results in disfunction and structural changes of mucosal coat of upper gastrointestinal.

Therefore, new treatment options for post- laparoscopic cholecystectomy pathological distresses are being searched for until now. Great attention is paid to investigation of drug-free methods of treatment. In this context, the use of mineral water is of significant interest as the most physiological one, possessing a wide variety of pathogenetic actions, while lacking any counter-indications and side-effects.

Aim of research was to investigate the efficiency of cholelithiasis post-laparoscopic cholecystectomy patients rehabilitation treatment with the use of Polyana Kupil' carbon dioxide medium-mineralized hydrocarbonate natrium bohrium mineral water, on the basis of diagnosis of structural and functional state of upper gastrointestines.

Matherial and Methods.

In the course of 2005-2010 we had 142 patients under the care, who had undergone a planned laparoscopic cholecystectomy for chronic calculous cholecystitis. The average age of the patients was 43+-2 years, range 14-75, women making up 88% of the survey sample. For the purpose of long-term results evaluation, 82 patients were examined, who had undergone laparoscopic cholecystectomy from 1 to 5 years prior the examination. The patients were divided into two groups. 42 patients in group I underwent rehabilitation treatment course in "Polyana" health resort. 40 patients in group II didn't undergo any rehabilitation treatment after cholecystectomy.

The rehabilitation treatment course lasted 24 days, involving use of Polyana Kupil'mineral spring water, warmed up to 38 C, 3-4 times a day ante cibum, Pevsner's diet #5, mineral bath, massage.

The quality of treatment was evaluated using R.Peterli modified Visick grading scale.

Besides general physical examination, all patients underwent ultrasound investigation of abdominal cavity organs and oesophagus gastroduodenoscopy, supplemented by gaster mucosal coat biopsy.

Results and discussion. In group I, the long-term result on Visick scale was evaluated as excellent in 25 patients (59.6%), good in 12 patients (28.5%), satisfactory in 5 patients (11.9%). In group II, excellent result was evaluated in 17 patients (42,5%), good in 11 (27.5%), satisfactory in 9 (22.5%), unsatisfactory in 3 (7.5%).

Abdominal pangs were registered in 16 (69.5%) of the patients in group II, and only in 4 patients in group I. The most common complaints of group II patients included postprandial abdomen heaviness (30.4%), weight loss (17.3%), pyrosis (26.0%),

corpostasii (7,5%). The latter symptoms were not registered in group I patients, who had undergone rehabilitation treatment course in "Polyana" health resort.

Pathological symptoms in group I and II patients were mainly caused by impaired motor-evacuation function of gaster and dodecadactylon (22% and 33% respectively), erosive gastroduodenitis (22.2%), duodenal bulb ulcer (5.55%), psychosomatic disorders (11.1%), chronic hepatitis (11.1%).

While gastritis was endoscopically diagnosticated in 67.7% of the patients admitted, rehabilitation treatment course reduced this quota to 7.1% ($p<0.05$), which is attributable to "Polyana Kupil'" mineral water buffer properties, as well as its normalizing effect on gaster acidogenic function.

Prior to rehabilitation treatment course, H.pylori had been detected in gaster mucosal coat biopsy samples of 67 (47.1%) gastritis and non-gastritis patients. Early postoperative rehabilitation facilitated H.pylori eradication in about 50% of the patients, which promoted excellent and good (Visick 1-2) results in 88% of the patients after laparoscopic cholecystectomy.

Conclusion

Rehabilitation treatment of cholelithiasis patients with the use of Polyana Kupil' carbon dioxide medium-mineralized hydrocarbonate natrium bohrium mineral water promotes normalization of motor-evacuation, acidogenic gaster and dodecadactylon functions, more effective H.pylori eradication, and may be recommended as an effective means of post-cholecystectomy syndrome prevention.

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Structural brain changes in teenagers with essential arterial hypertension

I.V. Plotnikova, V.Yu. Usov, M.P. Plotnikov, I.A. Kovalev

Introduction:

Brain is one of the target organs which can be affected by arterial hypertension (AH). Cerebrovascular disturbances determine the future of the patients with this disease as the latter is the most important reason of embolization [1, 2, 3, 4]. The magnetic resonance image (MRI) is the method of significant value to disclose different forms of cerebral pathology in patients with AH [5, 6, 2]. Home researchers think [5, 7] the following three main features: vascular disturbances in the form of lacunar infraction with perifocal zone; hydrocephalus (ventricular system and arachnoid cavity) are the MRI equivalents of hypertonic cerebropathy area); intracranial hypertension (periventricular edema, sulcus dilation, disturbance of grey and white matter differentiation).

There are data about structural brain disturbances with indices of daily-monitoring of arterial pressure in AH pts, it concerns mainly people older than 50 years [3, 8, 9]. Similar researches are not numerous in children and teenagers; they concern, in most cases, patients with heavy AH of symptomatic nature [10, 11, 12, 13]. Analyzed literature didn't show state study of brain structure in children and teenagers at the early stages of AH formation. Taking into consideration the fact that brain, parallel with heart, kidney, is a target organ with this disease, search for early markers of its structure change is of current importance.

The aim of the work:

To study the prevalence of structural changes of brain with the help of MRI data in teenagers with essential AH and to assess their connection with data of 24-hour blood pressure monitoring, Echo results and laboratory indices of endothelial function.

Methods:

150 teenagers with essential AH at the age of 12-18 years old (112 youths and 38 girls) were examined. The average age of patients was 14,9±2,0 years. BP increase higher 95% for correspondent sex, height and age was recorded at follow-ups 10-14 days apart. Patients with symptom AH forms and those who got antihypertensive drugs at the moment of planned examination were not included into the research. The control group contained 12 healthy teenagers.

All the patients were performed 24-hour blood pressure monitoring according to established procedure [14]. The following study groups are as the result:

1 group – 44 (29,4%) pts with "white coat hypertension" (WCH) – time index (TI) of systolic pressure (SP)/diastolic pressure (DP) wasn't more than 25%, indices of office pressure were higher then 95 ‰ of distribution for correspondent age, height and sex;

2 group – teenagers with liable arterial hypertension (LAH) – 50 pts (33,3%) – TI SP/DP was in the limits of 25-50%;

3 group – teenagers with stable AH (st AH) – 56 pts (37,3%) – TI SP/DP was higher 50%.

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MRI of brain was performed at MR-imaging unit "Magnetom-OPEN" ("Simens AG", Germany) which has resistive magnet with magnetic field 0,2 Tesla. Impulse sequence "Spin-Echo" was used for receipt of T_1 and T_2 weighted images. Sections thickness was 6 mm. Visual quantitative and qualitative analysis of obtained data. Presence and intensity of MRI intracranial hypertension manifestations, disturbances of cerebrospinal fluid circulation and cerebra vascular ischemia areas were assessed. Crebrospinal fluid circulation disturbances were established with increase of normal linear sizes of liquor contained structures according to literature data [6].

Status of left ventricle (LV) function and central hemodynamics were assessed according to Echo in M- and B- regimes with the help of ultrasound scanners "Ultramark 9 HDI-ATL" (USA) and "ASPEN" (Acusion, USA) according to standard practice [15]. We took measures and valued standard indices of systolic LV function, sizes of left atrium (LA). Left ventricle myocardium mass (LVMM) was assessed according to the formula (offered by R.B. Devereux [16]). LV hypotrophy in teenagers was diagnosed in a case when index of LV myocardium mass (ILVMM) ($g/m^{2,7}$) increased 95 ‰ of distribution for correspondent sex [17].

Activity of von Willebrand factor (vWF) was defined in vitro with the help of set of reagents ("Technology Standard" Barnaul). The method is based on vWF capability to cause agglutination of platelets with ristomycin [18]. Normal values range was in the limits of 50-120%.

Methods of multivariant modeling were used at statistical processing [19]. Quantitative variables with mistakes were used in their description. Quantitative variables are presented as frequency of occurrence and percentage ratio. Covariance analysis was used to assess difference between quantitative variables. The results are presented as the difference of means between groups and its 95% confidence interval (95% CI). Logical regression was used to analyze quantitative data. Correction for sex and age was made in the process of analysis. The control group was used as a referent group. Group comparison was made on the basis of 95%CI analysis. The critical level was p=0,05 [19]. Calculations were made with the help of statistic packages SAS v9.1 and R v2.7.0.

Results and discussion:

Mean figures indices of sizes of liquor contained brain

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Table 1. Mean figures indices of sizes of liquor contained brain spaces and volume of lateral ventricles according to MRI in teenagers with essential AH and control group

Indices	Statistical parameters	Control group n=12 (1)	WCH group n=44 (2)	LAH group n=50 (3)	St. AH group n=56 (4)	Intragroups p
Front horn of right ventricle, mm	Mean(SD) Median[Q1:Q3]	2,5(0,8) 2[2,3]	3,3(1,6) 3[2:4]	4,1(1,6) 4[3:5]	4,2(1,6) 4[3:5,5]	0,001
Body of right ventricle, mm	Mean(SD) Median[Q1:Q3]	3,8(0,9) 3,5[3:4,2]	5,0(1,4) 5[4:6]	6,0(1,7) 6[4,2:7]	6,2(1,3) 6[5:7]	<0,0001
Posterior horn of right ventricle, mm	Mean(SD) Median[Q1:Q3]	6,8(1,1) 7[6:7,2]	8,3(2,2) 8[7:10]	9,4(1,7) 9[8:10]	9,8(1,7) 10[9:11]	0,0018
Front horn of left ventricle, mm	Mean(SD) Median[Q1:Q3]	2,5(0,8) 2[2:3]	3,3(1,7) 3[2:4]	4,1(1,6) 4[3:5]	4,2(1,7) 4[3:5,5]	0,0022
Body of left ventricle, mm	Mean(SD) Median[Q1:Q3]	3,8(0,9) 3,5[3:4,2]	5,0(1,4) 5[4:6]	6,0(1,6) 6[5:7]	6,2(1,2) 6[6:7]	<0,0001
Posterior horn of left ventricle, mm	Mean(SD) Median[Q1:Q3]	6,8(1,1) 7[6:7,2]	8,2(2,1) 8[7:9]	9,3(1,8) 9[8:10]	9,6(1,9) 10[8:11]	0,003
Volume of lateral ventricle, mm	Mean(SD) Median[Q1:Q3]	7,9(2,7) 7,2[6,4:8,5]	11,0(6,1) 9,6[7,5:12,5]	16,1(6,6) 15[11,5:19,5]	17,5(5,5) 16,7[14:19,9]	<0,0001
SAS of convexity, mm	Mean(SD) Median[Q1:Q3]	2,0(0.0) 2[2:2]	2,2(0,5) 2[2:2]	2,2(0,4) 2[2:2]	2,4(0,6) 2[2:3]	0,046
SAS of posterior fossa, mm	Mean(SD) Median[Q1:Q3]	4,5(0,7) 4[4:5]	5,0(0,7) 5[5:5]	5,3(0,9) 5[5:6]	5,9(0,9) 6[5:6]	0,0011

Note: SAS – subarchanoid space

spaces and volume of lateral ventricles according to MRI in teenagers with essential AH and control group are presented in the Table 1.

As Table 1 shows gradual increase from the first to the fourth group was observed. Either average figures of linear sizes of lateral ventricles or indices of their volume increased. It should be paid attention to symmetrical increase of linear sizes of left and right lateral ventricles as this is characteristic for patients with AH [20].

Presence of significant differences only in groups of teenagers with liable and stable AH (table 2) was marked in difference analysis of average means of the given indices between study groups in relation to control with correction for sex and age.

Difference of average figures of analyzed values in relation to control was unreliable in the group of patents with WCH. An exception was the average difference of linear sizes of lateral ventricle bodies; it was a bit higher in this group than in healthy people. Average figures difference of sizes of SAS posterior fossa between study groups in relation to control with correction for sex and age in all study groups was clinically significant (table 2). At the same time sizes of SAS of convexital brain space were a little lager in teenagers with stable AH than in healthy counterparts (table 2). We

Table 2 Mean figures difference of linear sizes of liquor contained brain spaces and volume of both lateral ventricles according to MRI between control group and study groups with correction for sex and age

Indices	WCH – control gr. (95%CI), p	LAH – control gr. (95%CI), p	St.AH – control gr.(95%CI), p
Front horn of right ventricle, mm	0,97(-0,16 : 2,11) , p=0,093	1,84(0,68 : 3), p=0,002	1,88(0,75 : 3,01) , p=0,0013
Body of right ventricle, mm	1,42(0,4 : 2,43) , p=0,0065	2,35(1,32 : 3,39) , p=<0,0001	2,53(1,52 : 3,54) , p=<0,0001
Posterior horn of right ventricle, mm	1,13(-0,2 : 2,46) , p=0,096	2,19(0,83 : 3,55) , p=0,0018	2,58(1,25 : 3,91) , p=0,00018
Front horn of left ventricle, mm	1,01(-0,15 : 2,18) , p=0,089	1,89(0,69 : 3,08) , p=0,0021	1,91(0,75 : 3,08) , p=0,0014
Body of left ventricle, mm	1,42(0,42 : 2,43) , p=0,0059	2,41(1,39 : 3,44) , p=<0.0001	2,56(1,56 : 3,56) , p=<0,0001
Posterior horn of left ventricle, mm	1,07(-0,32 : 2,46) , p=0,13	2,13(0,71 : 3,54) , p=0,0035	2.,46(1,08 : 3,84) , p=0,00058
Volume of lateral ventricles, ml	3,05(-1,33 : 7,43) , p=0,17	8,42(3,95 : 12,89) , p=0,00028	9,49(5,15 : 13,83) , p=<0,0001
SAS of convexity, mm	0,15(-0,22 : 0,52) , p=0,42	0,15(-0,22 : 0,52) , p=0,44	0,4(0,04 : 0,76) , p=0,031
SAS of posterior fossa, mm	0,79(0,17 : 1,42) , p=0,013	1,07(0,44 : 1,7) , p=0,0011	1,71(1,09 : 2,32) , p=<0,0001

Note: p – significant differences with control group

are inclined that size increase of SAS of occipital area is not coincidentally. Some researchers, who study structural brain disturbances in children and teenagers with heavy AH, mark that the most often changes of brain structure influence on exactly occipitoparietal area [11, 13]. We can only suppose that area of posteria fossa is the most sensitive to BP increase, and exactly this area is the one where hypertensive encephalopathy (HE) starts to develop. Our results show that, besides SAS of posterior fossa enlargement, linear sizes of ventricular system increased as far as AH progressed. This fact is HE indirect indicator [21]. Intracranial hypertension is one of the MR-tomographic equivalents of HE. It manifests as periventricular edema or leukoaraiosis, sulcus enlargement and disturbances of gray and white substances differentiation [7]. Only minimal manifestations of periventricular edema were disclosed in teenagers with essential AH. It was presented as small diffuse edema of white substance around front horns of lateral ventricles and occurred in 54,6% of cases.

Frequency of occurrence of structural brain disturbances among our patients was analyzed. No disturbances in brain structure were observed in 26% of teenagers with essential AH. According to MRI increase of linear sizes of liquor contained brain structure was diagnosed in 74% patients from study groups and in 3,4% teenagers from the control group. Thus, isolated ventricular system dilation was disclosed in 19,3% teenagers with essential AH at different stages of its formation. This feature was defined in 15,9% teenagers with WCH, in 24% - group with liable AH and in 17,9% - group with stable AH. Combined dilation of lateral ventricles and SAS of occipital area was observed in 34,6% examined teenagers. The given combination was disclosed in 9,1% in WCH group, in one third of examined teenagers – liable AH group and in 58,9% - stable AH group. As it was mentioned above, periventricular edema was disclosed in 54,6% teenagers with essential AH. It is one of the features of intracranial hypertension. It combined with isolated dilation of lateral ventricles in 20% of cases among our patients, in 8,9% - with isolated dilation of SAS of occipital area and in 71,1% with combined dilation either of lateral ventricles or SAS of posterior fossa.

Severe HE manifestations were absent among our patients. Nevertheless we tried to divide nominally tomographic HE manifestations into two types of changes: minimal and moderate. We regarded the presence of isolated dilation of lateral ventricles or SAS of occipital area in combination with periventricular edema or without the latter as a minimal HE manifestation, and the presence in a patient all three analyzed features of structural brain disturbances as moderate.

Thus, minimal HE manifestations were disclosed in 49,3%, and moderate – in 24,7% teenagers with essential AH at different stages of its formation. In WCH group minimal HE manifestations were observed in 30,6%, moderate – in 4,5%, in liable AH group – in 46% and 32%, and in stable AH group – in 60,7% and 33,9% correspondently.

It was showed in many sources that cerebrovascular disturbances in adult, particularly, hydrocephalic changes, sings of intracranial hypertension, lacunar infarctions positively correlate with 24-hour blood pressure monitoring, namely, with average BP figures, with indices of average and pulse pressure and with exercise test with high pressure during day and night [2, 3].

In our research we discovered in the process of covariance analysis that indices of average BP during day and night and exercise test with high SBP nightly make significant contribution into size increase of SAS of posterior fossa. Thus, the latter (by 0,14 mmHg CI ((0,02:0,46), p=0,032) is marked at increase of average BP during the day for 1 mmHg, and increase of SBP time index by one unit (%) nightly entails increase of the same parameter by 0,09 mm CI ((0,01:0,16), p=0,028). Investigations, devoted to study of structural brain disturbances in children and teenagers with severe AH, showed that high BP leads to disturbances in the form of focal edema namely in occipital and occipitoparietal regions of the head, which completely disappeared after hypertensive therapy and normalization of BP figures [11, 12, 13]. Our results correspond to these literature data in the fact that namely posterior fossa is the very structure of brain, which the first respond to BP increase.

There is a connection between target organs, involved in pathologic process, with essential AH. Thus, K. Kohara et al. [22] disclosed that LV hypertrophy, along with systolic BP, is a predictor of cerebrovascular disturbances even without neurologic changes. In our study we got interesting results about correlation namely structural brain disturbances and a set of echocardiographic and vascular parameters. Performed covariance analysis disclosed correlations between subarachnoid convexital space, volume of lateral ventricles and morpho-functional parameter of the heart. Thus, increase of LVMM and ILVMM by 23,87g CI ((8,06:39,68), p=0,0033) and 5,71g/$m^{2,7}$ CI ((2,02:9,4), p=0,0027), correspondingly, is marked with increase of SAS of convexital space by 1 mm. Increase of lateral ventricles volume by 1 ml is accompanied by LA sizes increase by 0,9 mm CI ((0,06:1,74), p=0,036). Besides, it was discovered that sizes increase of right and left front horns of ventricles by 1 mm is accompanied by level rise of pulse pressure during 24-hour by 2,59 mmHg CI ((0,17:5,01), p=0,036) and 2,61 mmHg CI ((0,08:5,15), p=0,043) correspondingly.

All the researchers in this field think that disturbances of autoregulation of cerebral blood flow and endothelial dysfunction play great role in pathogenesis of brain damages in children and teenagers with sever AH [11, 13]. Taking into consideration this fact we tried to discover these interactions with the help of covariance analysis. We didn't discover significant differences in analysis of connections of laboratory indices of endothelial function markers and linear sizes of liquor contained brain spaces. However the following results were received in analysis of the same markers with quantitative parameter – the presence of HE. The difference of mean values of vWF level in the group with essential AH and HE presence was significantly higher than in the group of patients without structural brain disturbances and correspondently was 18,83% CI ((2,39:35,28), p=0,025). Besides vWF increase in the group of teenagers with HE, higher indices of intraventricular septum (IVS) and LVMM were marked. Thus, difference of mean values of IVS thickness and LVMM indices between groups of patients with HE and without it taking into account sex and age was 0,65mm CI ((0,13:1,16), p=0,014) and 18,15g CI ((4,32:31,99), p=0,01) correspondingly.

Analyzing received data, we can suppose that, apparently, changes in brain structure with AH begin earlier than disturbances in the structure of other target organs. This fact explains received correlations.

We tried to assess correlation between presence of perinatal affection of central nervous system (diagnoses from out-patients medical records) and structural brain disturbances in teenagers with essential AH. Here we didn't receive any significant correlations (p=0,050) and, most likely, it was connected with the fact that this aspect wasn't reflected in medical records.

Conclusion:

Structural brain disturbances in the form of size enlargement of its liquor contained spaces, which can be interpreted as early markers of its damage, were disclosed in teenagers with essential AH at different stages of its formation. Indices of average BP during 24-hour and time index of SBP nightly make significant contribution into formation of structural brain disturbances in the form of enlargement of subarachoid space of occipital area which is the primary substrate in disturbances chain of liquor contained spaces, appearing with high BP. We suppose that changes of brain structure start earlier than in structures of other target organs. This fact is confirmed by data of covariance analysis which showed that changes of linear sizes of liquor contained brain structures accompany by LVMM, LA sizes enlargement and increase of pulse pressure level. We didn't find similar works in the world literature so the received results are controversial and require further study and discussion. That allows finding new solutions in damage preventing of one the target organs – brain.

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Principal component analysis and correlative adaptometry used in estimation of human's immune system, suffered from allergic rinosinusopatia, complicated or not complicated by chlamidiosis

Liudmila Pokidysheva[1], Irina Ignatova[2]

The immune system is very important in overcoming the influence of harmful factors by human organism. This is one of the three integrative systems of the organism, which provides maintenance of homeostasis together with the nervous and endocrine systems [1].

The immune system is a unique natural protective mechanism. Due to the coherence of the entire functional immune system, the organism is able to confront to a number of factors that have a negative impact. Feature of the immune system is that it contains a regulatory function, capable on the presence of each specific antigen (which is the starting point of the disease) to answer by specific immune response in accordance with its individual characteristics [2, 3].

We have considered the adaptive response of immune system for exposing to the organism Chlamydia infection (CI). Mostly young people, who have just entered a period of sexual activity, are ill by Chlamydia. Strong tendency to increase the etiologic significance of intracellular pathogens (Chlamydia, mycoplasma, ureaplasma) and fungi Candida, obviously, can be explained by the evolutionary processes in the microbial world [4-6]. Pathological process may affect different organs and systems, including the eyes, upper, middle and lower respiratory tract, genitourinary system, urinary tract, cardiovascular system, liver and biliary tract, lymph nodes, joints, etc.

The frequency of mucosal lesions CI nasal passages is caused by the rapid increase in the prevalence of acute and chronic diseases of the nose among the child and the adult Russian population [7-10].

The given variety of parameters in peripheral blood cells, reflecting the state of the immune system, the need of application of statistical methods for data processing is evident. One of these approaches can serve as principal component analysis [11, 12], allowing to replace the initial interrelated features on a certain set of uncorrelated parameters, and describe the object by a smaller number of indicators.

The principal components define the factor structure of the phenomenon, which is characterized by the correlative coefficients between features and principal components. The internal structure of phenomena does not characterize features themselves, but characterizes the internal factors and properties, which is inherent of this set of objects. They are not always directly measurable. Having obtained these coefficients, we can see, what features perform a dominant role under the harmful effects of CI.

The method of correlative adaptometry allowed estimating the changes of the immune system during stress adaptation not according to the ideas themselves, but according to their correlation.

The immune system can be represented as a set of interacting subsystems. The principal components method was used for studying the structure of the relations between

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indicators of subsystems immunity tension: peripheral blood cells (first subsystem), CD-cells (second subsystem), general immunoglobulin (third sub-system) depending on the presence of CI and without it. When analyzing the groups of adaptive systems to the effects of chlamydial infection, we identified patterns of adaptation and the role of each subsystem (group of cells) with Chlamydia being present and without it.

Previously, we studied the adaptive capacity of blood cells patients with the Allergic Rinosinusopatia (AR), which is increased by chlamydia and without it. The adaptative processes of blood cells, CD-cells and immunoglobulins in general during the exacerbation and remission of various pathogenetic forms of AR were investigated by correlative adaptometry. The method is based on the effect of increasing the correlations and variances between indicators in the adaptative response to the impact of harmful factors and decreasing successful adaptation or termination (blocking) of such effects [13-17].

The analysis of pair correlative parameters of cells was conducted for all variable parameters for a period of exacerbation, remission, for all the groups. The number of reliable (most probable) correlations between the total number reflected the correlative coefficients, and the of these links were determined. The degree of connectivity options was estimated using the weight of the correlative graph, which is calculated as the sum of weights of its edges (the sum of the coefficients of pair correlations).

$$G = \sum_{|r_{ij}| \geq \alpha} |r_{ij}|$$

where r_{ij} - the coefficients of correlation between the

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i-th and j-th performance, α is determined by the level of confidence r_{ij}. We have taken into account only the significant coefficients of correlation values, which are greater than α or equal to α.

For analyzing the values of pair correlations between the indicators we have identified certain patterns of voltage changes in immune system cells, as evidenced by the weight dynamics of the correlative graph.

According to the method of principal components, each internal factor can also be represented as a function of the observed symptoms. Thus, we can move on to new integrated quantitative indicators of a generalized properties, which were involved in this factor. In this case, the functional immune system can be represented as a set of interacting subsystems of cells.

The relationship between indicators is greater under conditions of extremely harmful factors. With a strong correlation of the initial signs of all the variability is concentrated in the first l factors. Therefore, setting the proportion of total variance, which should be attributed to the first l components (typically 80-95% of the total variance of symptoms), we can compare the group by the number l of the first principal components.

We examined 305 people of eastern Siberia (70 - for men and 235 women) being 15-79 years old. There are patients with AR and CI being present and without it. The immune system was evaluated by classical indices, reflecting the cellular and humoral immunity. Laboratory studies conducted by Ph.D. A. Savchenko and laboratory-physician D. Rodina (State Institution Research Institute of Medical Problems of the North).

Our studies have shown certain regularities of changes in the correlative graph (with a total value of the relationship between the indicators were taken into account the correlation coefficients greater than 0.5), being dependant from the pathogenic forms and stages of AR. Traces the dominant role of lymphocytes and total immunoglobulin compared with other blood cells in restoring homeostasis of patients with AR mixed genesis.

When AR is complicating by the chlamydial infection organism involves adaptative resources, ensuring the restoration of all the morphological and functional parameters of blood cells, so it shows the increase of the correlative graph weight. Restoration of normal functioning of all blood cells and lymphocytes separately and common antibodies accompanied by a decrease of the correlative graph weight. Consequently, the removal of the above pathological processes leads to significant improvement in the status and tension release in the body's immune system.

The analysis of the correlative graph dynamics of blood cells, CD – cells and total immunoglobulins in patients with AR, non-infected by Chlamydia, showed a significant decrease in its weight to the indicators of CD-cells and total immunoglobulin ($p < 0,05$).

The correlative graph reflects the degree of accumulation of metabolic toxins within the cells and, consequently, the degree of structural and functional abnormalities of blood cells as well as CD-cells. The organism of the patients with chlamydia is caused by (involves) additional resources, ensuring the restoration of all the morphological and functional parameters of blood cells, the tension increases, and so the value of the weight of the correlative graph increases.

The investigation has shown that the AR chlamydial infection, although it is not the primary etiologic agent of the AR, but implies extra stress on the organism, adding to the disruption of homeostasis (the structural and functional abnormalities of cells).

Results. We calculated the total variance of all components and the contribution of each component in the total variance were, estimated the number l of the first principal component and calculated the variance explained by these components for all groups.

The most significant contribution is the first principal component (its contribution to the overall variability is 30%).

The first principal component correlates with all treatment of the symptoms, but the greatest influence on its magnitude (strong correlation - positive and negative) presupposes the presence of CD-cells (lymphocytes).

The biggest factors are peripheral blood cells in the second main component.

In general, the projection of multidimensional data onto the plane of the first two principal components is presented as a cloud (Figure 1).

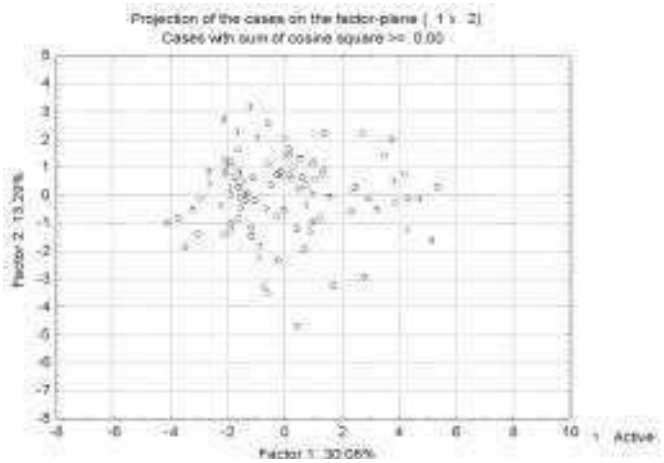

Figure 1. The projection of multidimensional data (patients with RA) to the plane of the first two principal components.

The below figure. 2 shows that the leading role in the adaptative process of the immune system in AR without CI play of CD-cells.

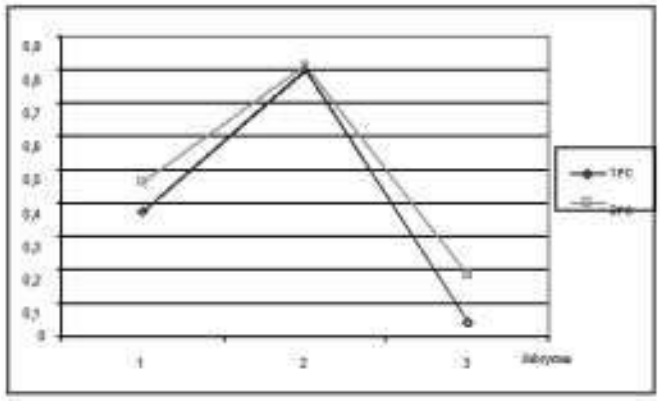

Figure 2. The integration of individual subsystems of immune system for the first (1 PC) and the second principal component (2 PC) in patients with AR. 1 - a subsystem of peripheral blood cells, 2 - Subsystem of cell lymphocytes, 3 - Subsystem of cell immunoglobulins.

The picture changes dramatically when burdening AR by Chlamydia infection. For this group, the proportion variance explained by the first seven principal components is equal to 94.4%

The share of the first principal component is 31,3% for this period. The correlation of the main component of CD-cells increases.

In the second principal component with the largest correlation coefficients included indicators IgA, IgM and IgG.

While applying the projections of multidimensional data onto the plane of the first two principal components (Figure 3), they are stretched along the second factor.

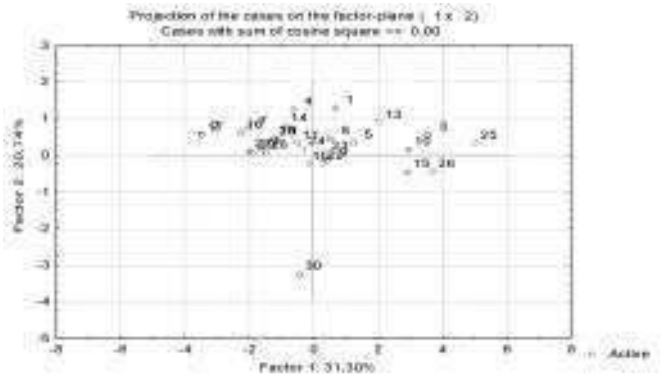

Figure 3. The projection of multidimensional data (patients with AR, increased by CI) to the plane of the first two principal components.

The dominated role belongs to the subsystem of immunoglobulins (Fig. 4). It should ensure the adaptative process and the resources to overcome the stress state of the organism. The second principal component can be called a

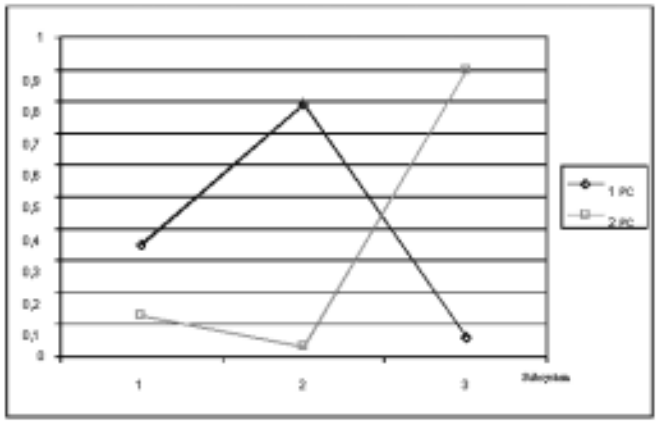

Figure 4. The integration of individual subsystems immune system for the first (1 PC) second (2 PC) of the main component in accordance with AR, increased by CI. 1 – A subsystem of blood cells, 2 – Subsystem of cell lymphocytes, 3 – Subsystem of cell immunoglobulins.

factor of immunoglobulins.

Conclusion. These results corellate with earlier studies by the correlative adaptometry [13], but it reveals the dominant role of immunoglobulin fractions in the protective adaptation processes to Chlamydia in patients with AR. The analysis of factor structure revealed the hidden patterns of adaptative mechanisms of the immune system of patients with AR with chlamydia and without it.

Principal component analysis allowed to describe the internal factors that determine the dominant role of the individual subsystems of immunity at the cellular level, with the AP, is burdened by chlamydia, the periods of compensatory interactions.

The method of correlative adaptometry allowed estimating the strength of the immune system in AR and consider at the mechanisms of adaptation at the cellular level deeper.

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Active regulation and control of physical parameters of water as a basis of a living organism. Biophysical aspects. Biophysical model of a living organism. Accelerated organism restoration after an intense load in sport

Sergey Postnov

Development of this research line started from the piece of evidence obtained in 1984 in Central Aerohydrodynamic Institute within the limits of the research of flow over an underwater high speed object. This research had nothing to do with biology or medicine. However, later it turned out to have become a basis for a new concept in biology and medicine and let us look at biophysical processes of a living organism in a different – non-conventional - way from the viewpoint of physics, biology and medicine.
The research was carried out by the leading institutes of the Russian Academy of Sciences and Russian Academy of Medical Sciences and is aimed at studying biophysical water properties and the way it affects living bodies.
The experimental evidence shows that there is a boundary layer in the water/surface system not only in a classical case, i.e. in a flowage, but also in still water. The boundary layer water has a number of particular physical properties.
It has been proved that water in a living organism (blood plasma, lymph, intercellular and intracellular liquid) can only be in a boundary layer state. Not in the form of gel or in a glassy state, but exactly in boundary layer state. This fact explains the difference between physical parameters of water in a living organism from the ones of water we drink.
We have offered explanations of the physical mechanism of boundary layer formation both in a living organism and on abiotic surfaces at the distance of 0-350 μm from the surface forming a boundary layer.
There is an experimental evidence that proves the hypothesis that physical parameters of body liquid including blood plasma, lymph plasma, intercellular and intracellular liquid (let us call it further in this article "body liquid") are the parameters which determine the course of biochemical reactions in a living organism.
Another experimental evidence proves the hypothesis that by changing physical parameters of body liquid one can control and determine both biochemical reactions and general biological processes taking place in the organism.
There was elaborated a technology which allows to change physical parameters of the liquid inside a living organism.
A lot of biological and medical research has been done on human cell cultures, laboratory animals, apes. By the example of volunteers the mechanism of body liquid physical parameters change has been studied as well as the way this change affects biological, biochemical and medical processes of a living organism.
A biophysical model of a living organism has been offered on the basis of the above-listed assumptions and a vast range of experimental evidences. This model represents an attempt to systemize the existing experimental material, to put forward hypotheses, to formulate the consequences for physical aspects of life of a living organism as a system.
The hypotheses and consequences have been formulated on the basis of classical biology and classical physics.
A technique for accelerated restoration of a sportsman's organism after intense physical activity has been elaborated on the basis of biophysical model of a living organism [1] which takes into account physical parameters of human body liquid. The physical definition of incomplete restoration of body has been given and proved, the extreme case called "chronic incomplete restoration syndrome" has been elicited.
A technique for diagnosing the above-listed conditions of a sportsman's organism has been worked out. Diagnostics and restoration methods have been tried on volunteer sportsmen – submaster sportsmen and masters of sports. Efficiency of the technique has been proved on volunteer world-class masters of sports and merited masters of sports, among them Russian national light athletics team members and candidates.

Introduction

In 1984 a team of scientists of Central Aerohydrodynamic Institute found out while studying air-water mixture flow over bodies that in a narrow layer of water adjacent to an object's surface, i.e. in the boundary layer, air bubbles were missing. In the same year it was found out that the boundary layer exists even in still water. It was also established that boundary water physical parameters were different from those of bulk water, i.e. of the water remote from an object's surface. For example, in a suspension the following regularity was detected: the closer to the surface the fewer solid particles per volume unit, next to the surface there were no solid particles at all. Prof. G. Pollack [5] obtained similar evidence 20 years later, moreover, he registered that electrical potential changed in a non-linear manner the closer it got to the surface. The analysis of the experimental evidence obtained in Central Aerohydrodynamic Institute showed that near-wall water of the boundary layer (further "boundary water") is very similar to human body liquid according to many of its physical parameters. This fact established at the end of the eighties became a starting point for research of boundary water phenomenon which resulted in building a biophysical model of a living organism which not only helps to explain a huge volume of experimental materials accumulated by scientists but also allows to forecast research results.

"Boundary layer theory" is a fundamental branch of gas and fluid mechanics and dates back to 1904 when the first boundary layer equations were published. The fact that boundary layer behaves almost like an autonomous object has been known for a long time as well as the fact

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that physical parameters of water in a living organism are different from those of bulk water. The experimental fact that boundary water parameters and parameters of water in a living organism are very close had not been explained until the biophysical model of a living organism was elaborated. It includes hypotheses and conclusions based on experimental data. The model consists of two parts - physical and biological - which are reflected in its name.

G. Pollack [5] says that water in a cell is a special jelly-like condition. As our research shows, water in a cell of a living organism is nothing special from viewpoint of physics - it is in a state of boundary layer water which has been studied in hydrodynamics for over 70 years.

Before passing over to biophysical model of a living organism, let us consider some biophysical aspects of the problem.

Some biophysical aspects of the problem to be solved

Methods of research:

- physical parameters have been measured with physical instruments;
- generally acknowledged methods of biology;
- medical methods approved by Ministry of Public Health of the Russian Federation.

Results are discussed, hypotheses are put forward and conclusions are made only within the boundaries of classical physics, classical biology and classical medicine.

In a living organism, ordinary water taken from environment goes through a range of changes which lead to changes of its physical properties. The water acquires the properties that support life itself in a living organism. The more evolved the organism is, the more significant the changes of water physical properties in it. In 1935 the biologist E. Bauer in his book "Theoretical biology" [7] put forward a hypothesis that an organism spends a lot of energy on changing physical properties of water. The recent experimental data proved that Bauer was right.

In ideal conditions an organism has enough power to transform potable water into an adequate aqueous medium and keep up the required physical parameters of body liquid. But real life is not that simple. The organism is exposed to external and internal factors such as low-quality food, irregularity of living, aggressive environment, viruses, bacteria, etc. An organism is compelled to spend its energy on counteracting negative external and internal factors. Unfortunately, its energy stores are limited. A moment comes when it cannot maintain its body liquid physical parameters as they should be, neither in a cell or in an organ, nor in an organism as a whole. At that moment serious problems start because biochemical reactions can be neither qualitatively nor quantitatively correct. According to research results, this leads to decrease of immunity, hypoxia, derangement of metabolism, etc., simultaneously with chronic fatigue syndrome aggravated with pathologic processes caused, along with other reasons, by virus infections and bacillosis.

A natural question emerges: if somehow for some period of time the body liquid physical properties that have been lost or weakened are restored, what will happen? The body will probably not need to spend its energy obtained by way of oxidative reactions on maintaining its physical properties. Consequently, it can, at its own discretion, direct the saved energy there where it is needed at this moment.

Objective of research: to prove by experiment the above presented hypothesis.

Before proceeding to this work we should answer the following question: how can physical properties of body liquid be changed at once? There are dozens of liters of liquid in a human being, this is not an ordinary liquid, this is a substance making a basis of life, substance in which sophisticated biochemical processes are going on all the time.

The question is far from being a simple one. But if biology and medicine manage at least partially to answer it what opportunities will open up: a human organism will become able on its own or with minimal interference from outside, for example, with the help of medicines, to immediately detect disorders in its systems and has all the necessary prerequisites for their efficient elimination.

It is impossible to obtain the same result with the help of medicines and chemical agents. The procedure of human body liquid correction resembles more physio procedure than drug therapy.

Solution turned up from where it was not expected.

Serious work in this direction was prompted with a piece of evidence obtained in mid-eighties of the twentieth century in Central Aerohydrodynamic Institute during studies of flow over objects moving under water at a high speed (submarines, torpedoes, etc.). It was established that in the thin water layer adjacent to the surface of the body moving under water (that is in the so called boundary layer) water acquired a number of physical properties which were fundamentally different from those of bulk water. These parameters can be regulated. Moreover, one can select surfaces in contact with which boundary layer water acquires the physical properties which are very close to those of blood plasma and human intercellular fluid.

It should be noted – and it is crucial - that change of physical parameters of water in the boundary layer develops itself in the same way like in a living organism from viewpoint of physics [1]. The physical mechanism of this phenomenon has been studied by now – this is epitaxy, in this particular case – growth of a liquid crystal of water on the substrate that is on the surface which is in contact with water.

The technique of separation of the water with changed physical and biological parameters from boundary layer has been elaborated by now [3]. This water, let us call it "Boundary water" or "Awoda", served as prototype of a preparation with which body liquid parameters were changed within the limits of the experiments.

Medical research was carried out according to classical algorithm: first on human cell cultures, then on laboratory animals, apes and, finally, volunteers.

The leading institutes of the Russian Academy of Sciences and Russian Academy of Medical Sciences continue doing this research.

Safety for a human-being and absence of side effects have been established during this research, a wide range of positive effects on a living organism have been identified.

The most important of them are as follows [2]:

- slowing down and even cessation of neuronal death process in brain (this process gets faster in the course of ageing of any mammal, including a human-being);
- a very powerful antiviral action which affects such viruses as human influenza virus, human pandemic influenza virus (swine influenza), herpes virus, oncovirus SV40, etc.;

- a very powerful immune stimulating and regulating action;
- a very good interaction with pharmaceuticals.

In some cases not just facts of therapeutic action of the preparation were established but its biological mechanism at the cellular level was disclosed, too [2].

It should be noted that according to research results, the elaborated technique or, to be more precise, physio procedure based on water extracted from boundary layer combines perfectly with all the modern medicines [2]. Moreover, the process of boundary water influence on a human body can be controlled with diagnostic systems used in medicine nowadays and can be regulated, too.

Good interaction with pharmaceuticals and health-improving preparations is explained by the fact that boundary water allows the body to function on a systems level, that is on the level of body systems – central nervous system, cardiovascular system, endocrine system, etc. Boundary water helps to overcome a lot of diseases, if a body has enough resources. But, unfortunately, in today's reality very few people have such resources, consequently, medicines and health-improving preparations are needed.

In this case medicines become much more efficacious [2] as the ground for their work has already been prepared with the help of boundary water. This fact was clinically proved.

The only rule is: medicines should be taken at least one hour after boundary water intake. Otherwise, the water is going to inactivate the medicines.

Besides systemic effect, the water from boundary layer has a range of its own therapeutic effects. Here are some of them:

- immune stimulating effect on cellular level;
- regulation of humoral immunity;
- marked antiviral action;
- recovery of nerve conduction;
- efficacy against hypoxia including hypoxia of brain and cardiac muscle;
- efficacious detoxication;
- restoration of negative charge in nuclei of cells and red blood cells;
- elimination of chronic fatigue syndrome, sleep restoration and metabolism normalization;
- many other effects.

The research results show that the most efficient form of intake is irrigation of tunica mucosa of mouth, the dose in this case is normally 0,1-0,5 ml.

An interesting fact is that negative charge is restored in cell nuclei with the help of boundary water. Prof. Shakhbazov, a Soviet scientist, elaborated in the eighties of the twentieth century a technique for assessment of physiological age according to percentage of negatively charged cell nuclei [8]. The technique is based on a vast experimental material collected by the scientist himself and his disciples. The technique helps assess biological age of a human being not just on a cellular level but on an intracellular one. It was proved that boundary water rejuvenates cells from viewpoint of their nuclei condition in an efficient way. The same happens to red blood cells.

One normally starts perceiving the effect of boundary water after a couple of intakes. There is one rule to be observed: taking in boundary water one should drink at least 1,5l of good quality bulk water a day and make sure that the body receives a sufficient amount of proteins, fats, vitamins, micro- and macro elements, etc.

Thus, boundary water intake creates conditions in which our body is able to restore itself and to cope with numerous diseases peculiar to a contemporary human being in a reasonable period of time if the body possesses enough inner resources. If the resources are not enough, medicines are needed. Even in complicated cases recovery happens much earlier than without boundary water use.

Physical aspect of the proposed biophysical model

In the water/surface system there is a near-wall layer about 300 μm thick in which instruments register a number of differences in physical properties in comparison with the environmental bulk water, such as higher electro conductivity, lower heat capacity, etc. Let us call the water from boundary layer "boundary water", while the environmental water – "bulk water". The differences in physical properties of these two water types grow more marked in a nonlinear manner the closer it gets to the surface.

Heat capacity of boundary water is lower than that of bulk water. Heat capacity from viewpoint of physics is a quantitative characteristic of a number of degrees of freedom of substance molecules or atoms. Thus, boundary water molecules have fewer degrees of freedom than bulk water molecules. This means that in the same conditions and in same volume of water, boundary water, i.e. water near wall, has geometrically more marked and long-lasting hydrogen bonds than bulk water. This allows to make the following conclusion:

Hypothesis: due to forming surface between the layers and in each layer of boundary water, boundary water intermolecular (hydrogen) bonds are stabler from viewpoint of decay period and more pronounced from viewpoint of geometry than bulk water intermolecular bonds.

Piece of evidence: the closer to the surface, the stabler intermolecular bonds.

As water has some properties of a crystal one can make a supposition: a number of degrees of freedom decreases under influence of the surface forming boundary layer. Boundary layer formation mechanism is a kind of a well-known process called epitaxy.

Hypothesis: from viewpoint of physics, formation and growth of water liquid crystal in boundary layer is a kind of epitaxy process that is growth layer by layer of a crystal body on a surface called substrate; the growing crystal body takes over the crystallographic form of the substrate.

This explains, for example, why properties of the same water in boundary layers near different surfaces have quantitative differences which were accurately registered. Just like properties of waters of different origins and chemistries are different in boundary layer near the same surface.

A crystal and a substrate can be made either of the same material or of different ones (heteroepitaxy) and this influences very much epitaxy process. In case of heteroepitaxy the process depends on difference between lattice constants of crystals. If the difference is over 10% (which is our case), some surfaces of the substrate lattice have no continuation in the lattice of the growing crystal. The edges of such broken surfaces make up dislocations, which leads to distortion and accumulation of errors in the lattice of the growing crystal. There are errors caused by collocations, too. Collocations are local lattice disturbances in the growing crystal stipulated by various reasons: here as well refers the fact that the growing

crystal is a liquid even though with the properties of a crystal, and it is still prone to Brownian motion and, as a rule, heterogeneous by its content because of dissolved chemical agents. Due to this, each subsequent layer is different by its crystal structure from the previous one, that is regular destruction of the crystal structure formed by the substrate takes place. This explains the nonlinear correlation: the farther from the surface the more similar boundary water properties to bulk water properties.

Existence of boundary layer with water properties changing in a nonlinear manner explains numerous pieces of evidence: for example, in frozen meat, part of water is frozen, another part is in the state close to amorphous, the rest of water doesn't get frozen; Another example – bound water and its properties. This hypothesis explains numerous pieces of evidence, like water in small capillaries, nanotubes, body cells being in a state close to "crystalline" and "glassy", "jelly-like" and others.

The above-listed pieces of information can be set out in the following theses:

a) near the surface adjacent to water there is a relatively thin water layer - boundary layer properties of which are different from those of bulk water in the environment;

b) boundary water properties depend on the surface material, origin of water and on the substances dissolved in the water;

c) the surface in contact with water determines formation of boundary layer;

d) boundary layer is a liquid crystal (as far as it can be applied to water) grown on the surface like on a substrate (heteroepitaxy);

e) the farther from the surface the weaker (in a nonlinear manner) boundary water properties and the closer they are to bulk water properties.

Biological aspect of the proposed biophysical model

Hypothesis: water in a living organism is only in the boundary water condition.

Prima facie in human blood supply system there is a lot of water: an average human being has approximately six liters of blood, of which three liters of plasma and three liters of red cells. Without allowance for other structures, such as vessel walls, etc., let us do some calculations. The total area of red cells surface is 3500 m^2. Three liters of plasma uniformly distributed on this surface make up liquid layer about 1 micrometer thick which is 0,3% of boundary layer height subject to registering with instruments (300 μm). Thus, even in a large vessel water exists in the form of boundary layer made up with red cells, vessel walls, etc. The same refers to intracellular liquid. The size of procariotic cells varies from 0,5 to 5 μm (1,7% of boundary layer height), while eukaryotic cells size varies from 10 to 50 μm (17% of boundary layer height). But one cannot make conclusions on the basis of absolute sizes because a cell is filled with cytoplasm which contains organoids (ribosomes, mitochondria, vacuoles, etc.), cell inclusions, a nucleus, genetic material in the form of DNA molecule, etc. Consequently, a typical size becomes much smaller because each biological object forms its own boundary layer on its surface. The boundary layer height in this case is close to that in blood.

Hypothesis: each biological structure forms its boundary layer, the properties of which depend on molecular and spatial characteristics of the structure.

Consequence: biological structures interact, along with other ways, through mutual impact of their boundary layers.

Hypothesis: Biological structures such as DNA, proteins, red blood cells, mitochondria, cells, organs, form their boundary layers with the properties which provide their optimal functioning. Boundary water properties of various biostructures differ from each other in a number of ways; in the course of a life cycle or a functional cycle the properties may change even within one and the same structure.

- The more differs the metabolism of cells, the more differ the properties of boundary water in these cells.
- Boundary water of a biostructure due to its physical properties is a powerful buffer which protects it from internal and external impacts.
- A vital task of an organism is to create and maintain "correct" properties of boundary water in each organ, cell, etc.

This hypothesis is proved with the following pieces of evidence:

- amount of physical solution which can be injected intravenously in a human body without negative consequences is restricted;
- water in a cancerous growth differs by its physical properties from water in a healthy organ [4];
- adding the boundary water "Awoda", properties of which are close to integral properties of human body liquid, to human cell culture leads to almost no change of the viability of continuous normal cells, causes drastic suppression of proliferation of various oncogenic cells after one passage and their complete degeneration after the second passage [2].

Any organic and inorganic structures coming inside an organism, whether they take part in metabolic processes or not, affect the properties of the body boundary water because they form around themselves their own boundary layer. Their influence can be many-sided.

A fault in molecular structure of any part of a cell threatens with distortion of its boundary water properties. Such a fault in several cells puts at risk the whole organ. The same refers to organic and inorganic substances which enter a body from outside and participate in cell metabolism. Their molecules form boundary water layers around themselves which can either favour or disturb vital functions of cells. From viewpoint of physics, an organ gets into serious trouble when it or an organism as a whole for some reason doesn't manage to correct faults in boundary water any more.

A converse effect might as well exist:

Hypothesis: restoration of physical properties of boundary water in any biological structure exposed to mutation, attack of virus, etc., leads to significant abatement of negative influence, mobilization of immunity, on all levels including a cellular one.

Hypothesis: restoration of physical properties of boundary water in a living organism results in restoration of biochemical and biological processes within the limits of its vital activity; restoration of its systems: nervous system, cardiovascular system, endocrine system, etc.

Currently there are numerous experimental evidences which prove these hypotheses.

Thus:

- water in a living organism is in boundary water state;
- boundary layer of an organism is manifold, rich of energy and has a number of unique physical properties and can be considered as an independent system which, along with circulatory system, lymphatic system, etc., can take part in a

number of physical processes in an organism;
- each biological structure of an organism forms boundary layer with optimal properties. These properties depend on molecular and spatial structure of a biostructure and water chemistry;
- besides other ways of interaction, biological structures interact through cross-effect of their individual boundary layers;
- interference in molecular and spatial structure of a biological structure causes changes in its boundary layer properties;
- there is a maximal limit of change in boundary layer water properties (a local one and a general one), if it is exceeded, irreversible changes take place in a living organism, on the level of a cell, organ or organism as a whole;
- a living organism spends incoming energy, along with other activities, on maintaining and restoration of boundary water properties;
- restoration of boundary water properties to the level (local and general) required by the organism results in significant abatement of negative influence, mobilization of immunity on all levels including cellular one, restoration of biochemical and biological processes within the limits of organism vital activity, restoration of its systems activity.

Acceleration of organism restoration processes after sports training load

Experimental check of a biophysical model of a living organism [1], taking into account physical parameters of human body liquid, was tested within the limits of elaboration of a technique for accelerated sportsman organism restoration after intense training load. The obtained experimental data have proved the hypotheses and conclusions regarding biophysical model.

Besides, a number of independent problems have been solved. Here are some of the solutions found:
- Physical definition of incomplete restoration of an organism has been given and proved, the extreme case called "chronic incomplete restoration syndrome" has been elicited.
- A technique for diagnosing the above-listed conditions of a sportsman's organism has been worked out.
- Diagnostics and restoration methods have been tested on volunteer sportsmen – submaster sportsmen and masters of sports. Efficiency of the technique has been proved on the examples of volunteer world-class masters of sports and merited masters of sports, among them Russian national light athletics team members and candidates.

It is known that intense training load is accompanied with drastic decrease of amino acid and carbohydrate content in a sportsman's organism. This is the consequence of intense muscle activity. Energy needed for this activity is worked out in any living organism in the course of oxidative reactions. During recovery of an organism, on the contrary, compensatory reactions prevail. Redox reactions are accompanied with redistribution of electrons among reducing and oxidizing atoms. Degree of electron activity in redox reactions can be regulated by way of changing value of redox potential, to be more precise - redox potential of aqueous medium where reactions proceed. Human body liquid (blood, plasma, intercellular liquid, etc.) are characterized by a negative value of redox potential. This indicator of chemical activity obviously plays an important role in vital activity of an organism. For example, arterial blood and venous blood differ from each other according to this characteristic.

The proposed technique for acceleration of organism restoration after training load is meant for regulating physical parameters of a sportsman body liquid and improving redox potential of organism aqueous medium, making compensatory reactions prevail.

Gas discharge visualization technology (GDV) [6] lets control current condition of a sportsman's organism and select an individual regimen of restoration. The principal parameter of a sportsman's condition which was checked with the help of GDV-camera was the area of glow in GDVgram of fingers (GDV-f). In a long series of measurements of sportsmen's GDV-f a direct relation between value of this parameter and functional condition of an organism was found out. For example, the parameter value declined during training and recovered after restoration. In some cases GDV-camera signal fell down to almost zero ("total breakdown"), for example after a heat and especially after a contest. Measurements were taken according to the following technique: area of fingers GDVgrams was measured during heats as soon as a 800 m sprinters had covered 600 m and stopped there to avoid organism acidulation. Measurements were as well taken before the heat and one time per hour in the course of several hours after the heat. In the second case – before a contest and immediately after it. A sharp decrease of the parameter value was registered. Thus, during heats its value decreased 1,5-2,5 times, while after contests – 2,5-4,0 times. Obviously, the bigger decrease during contests was caused by stress loads as well as extra 200 m which were not run by the sportsmen during heats. Sportsmen were observed after contests and it was noted that recovery process in a sportsman's organism doesn't start until fingers GDVgram area value has reached a certain level. This level is individual and, as we believe at the moment, depends on natural abilities of an organism. But original level (before contest) and speed of restoration is in direct relation with level and degree of a sportsman's preparedness. This correlation was discovered by comparing results of measurements of submaster sportsmen and merited masters of sports who have experience of contest participation.

Degree of restoration incompleteness was registered on the basis of GDV-grams as follows. GDV-f value was lower next day before training than before the training the previous day. The value changed 1,3-1,8 times. When the sportsmen were asked how they were, 100% of them replied "good" or "excellent". If training process was not corrected, after several training sessions the regarded parameter value went down faster and faster before each following training session. Maximal decrease was registered among submaster sportsmen, especially among very hard-working sportsmen, as coaches said.

Let us regard an example: GDV-f value of a well prepared sportsman is 20-22 thousand arbitrary units, after training session it falls down to 8-10 thousand units. The value of a sportsman who suffers from chronic incomplete restoration syndrome before training session can be 100-200 units, that is 100-200 times lower than the value of a fit sportsman. However, 100% of sportsman said they felt quite well or well. It should be noted experienced sportsmen - world-class masters of sports and merited masters of sports – answered the question "How are you?" in the same manner. In order to get a sportsman's organism out of this dangerous situation, one should change training process by way of easing-off

together with GDV-diagnostics and traditional physiotherapy. But this takes a long time during which no full value training sessions are possible.

To accelerate restoration processes, including the case of chronic incomplete restoration of an organism, there was elaborated a technique based on correction of human body liquid properties and aimed at accelerated recovery of its electron-donor properties.

This conception has been realized thanks to a preparation called "Awoda" obtained by way of extracting water from boundary layer. Awoda is produced by way of separation of mineral water into boundary layer water – water located near surfaces - and the rest of water – bulk water. Intake procedure – irrigation of oral cavity with pump doser. One-time dose for an average human being 0,1-1,0 ml, for a sportsman after training session – 5-10 ml. The elaborated technique and Awoda preparation allow to completely restore a sportsman's organism for the second training session during the day within the limits of training pattern 2 – 2 – 1 (two training sessions on the first day, two sessions on the second day, one training session on the third day). For 40% of sportsmen it was an adaptative training process. It should be noted that Awoda contains no additives and turns into ordinary water in a sportsman's organism. In the open air, according to readings of instruments, physical parameters of Awoda become the same as those of the original mineral water within 14-15 days. Awoda, according to the conclusions [2] resulting from research conducted by the leading institutes of Academy of Medical Sciences of the Russian Federation on human cell cultures, animals and volunteers, is characterized by heightened biological activity, in particular by powerful antiviral and immune stimulating action on all levels, including cellular one. Awoda application together with pharmaceuticals or health improving preparations and physio procedures open up a promising course in the field of biomedical technologies [2]. Restoration process can be controlled with diagnostic systems, such as GDV-camera, blood test, etc. On the basis of blood test results individual daily therapeutic dose of Awoda can be determined.

Two typical examples. A test group of sportsmen used Awoda according to the elaborated technique during intense training period with a lot of training sessions per day. In elimination competitions for winter championship of Russia each of 10 members of the group set a personal record. In a control group – two out of ten. Later the sportsmen of the test group selected for the winter championship of Russia in light athletics set personal records in this championship. Another example: world-class masters of sports, Russian national team member, who took Awoda (under 5 ml per intake) during the period of preparation for winter competitions, covered in winter international competitions 1500-meter distance in a period of time two seconds shorter than his personal record set in the previous summer season.

Thus, an efficient technique for restoration of a sportsman's organism after intense training load has been elaborated. Restoration process can be controlled and regulated according to readings of instruments and devices. If A sportsman takes Awoda for a long period of time and reaches a peak form of condition, it is recommended to test his/her blood as control method.

Restoration process is provided with the help of Awoda which is the water extracted from mineral water.

It was established that Awoda has independent therapeutic effects such as antiviral and immune stimulating. This leads to decrease of morbidity among sportsmen. It was experimentally proved that Awoda, by its mechanism of action, doesn't replace vitamins, microelements, amino acids, etc.

Conclusions

Physical parameters of body liquid can be actively influenced upon, thus can be regulated biochemical reactions and biochemical processes in general going on in an organism.

A technique of active regulation of human body liquid physical parameters has been elaborated. Its safety has been established.

Efficiency of the technique of active regulation of human body liquid physical parameters for human organism restoration and treatment and prevention of diseases has been experimentally proved.

Pieces of evidence show that the proposed biophysical model which implies that water inside a living organism is in a physical state of boundary layer water can be considered experimentally verified and has the right to exist.

The biophysical model not only explains the available pieces of evidence but also allows to forecast results of experiments.

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Cervical disc herniations: a new way of ultrasound diagnostics

Andrey Remnev, Andrey Oleynikov

Tool diagnostics of cervical disc herniations is reduced now to application of several basic methods: Computed tomography (CT or CAT scan) and Magnetic resonance imaging (MRI). These methods allow to establish the exact diagnosis. However often there are clinical situations when of cervical disc herniations it is necessary to apply absolutely others to diagnostics instrumental methods. What it are situations? First of all, it is necessity of depreciation of diagnostic researches, presence of contra-indications for carrying out CT or MRI, absence of the equipment for carrying out CT and MRI. What decision of this diagnostic problem can be? We just are in a situation when we can't all our patients with cervical disc herniations direct on researches CT or MRI. Besides, we need tool control of results spent treatments. Therefore we have developed some new ways of diagnostics of pathology of cervical and lumbar department of a backbone with the help medical sonography (ultrasonography). We do more than 4000 ultrasonic researches of lumbar department of a backbone every year. We applied ultrasonic scanner Aloka SSD-4000 ProSound PHD to researches with transducer 2,5-6,0 MHz. This experience has allowed us to develop a new method of diagnostics cervical disc herniations (in 2011 we have received the positive decision on delivery of the patent for the invention of the Russian Federation on this method). The essence of a way consists that at polyitem ultrasonic scanning in a mode of real time, define the forward size of the vertebral channel, and define the cross-section size of the vertebral channel, count size of an index of the vertebral channel the relation of the cross-section size of the vertebral channel to the forward size. Sensitivity our method has made 94,1 %, specificity has made 98,2 % (in comparison with MRI). At the same time ultrasonic research possesses a number of advantages in comparison with MRI. First, for carrying out of ultrasonic research there are no known contra-indications and the restrictions considered at carrying out MPT. Secondly, carrying out of ultrasonic research occurs in real time without step-by-step research (formation of cuts) to the further mathematical averaging of the received data. Thirdly, it is possible to carry wide availability of a method of ultrasonic research and rather low cost of diagnostic procedure to doubtless advantages.

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Thus, the way of ultrasonic diagnostics of cervical disc herniations allows to provide objective exact diagnostics of cervical disc herniations.

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Human civilization and medicine in the context of ecology

Bernhard Jakob Schaller

At present the human civilization is experiencing the upsurge due to the growth of informational and technical possibilities, great scientific findings in all fields of knowledge, development of new technologies. The XXI century can be characterized as an epoch of information, technological achievements and economic progress.

However there is no doubt that the present time is the epoch of deep ecological and cultural crisis: catastrophic destruction of the environment, the increase of ecological problems and radical reduction of "islands" of living nature not affected by a human activity. In socies life negative tendencies are increasing, the gap between developed and developing countries is proliferating, social exfoliation is continuing, and a wave of terrorism, in comparison with which even the consequences of natural cataclysms are fading, overflow the world communities. The very possibility of human existence on the Earth is under threat.

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Contradictions between science-technical progress and social–mental ones are deepening becoming more strained. In connection with that a question arises: why is the wheel of mentality in a complicated mechanism such as "mankind" blocking up? Why is mental evolution unlike science-technical evolution realized so slowly if at all becomes true? Looking back on the present situation in the world and acknowledging by what values a usual human being is guided, what principles he is practicing, what aims are hatching, what guiding lines he prefers there arise an impression that a human being's mentality is in a deep crisis.

The history once again proved that great scientific achievements can become an evil for the mankind justifying the saying that "knowledge itself does not always mean good" as it had been considered from Socrates time. Beyond the bounds of a social-moral use the scientific knowledge loses its cultural-humanistic dimension and leads to cynicism. It recognizes as necessary "a combination of virtue and learning", overcoming the frames of narrow gnoseologism and perception of the fact that human consciousness does not mean only knowledge. It is appropriate to mention here the following words of Jorge Hudges: "We have to think widely and acknowledge that human science by definition can study only those things available for scientific methods of research. There are no grounds to think that these methods can cover all existing".

The need to perceive the world as a whole, to form an integrated ecological image of the universe is keenly felt. In that respect a search of "a common theory of life" (P. Devis), interdisciplinary conception of life (P. Tayar de Sharden), integral idea of development (I. Prigozhin), universal evolutionism (N.N. Moiseev), an extended view on the world and on a human as bioecosocial entity (W. Kofler) are gaining the significance.

An interest to the method of constructing a pattern of the universe in categories of a historically developing human culture is growing (D. Lazer). Rapid progress of the role of the ecology in the field of education, science, culture, formation of ecological culture as a system of historically changing over-biological programs of human activity, harmonizing the attitude of the society to Nature is going on.

More than 10 years ago, in 1998 UNESCO program on ecology declared Moscow as a capital of "the World Day of Environment". Representatives of more than 50 countries, concerned by the state of the Earth claimed that the main reason of ecological crisis rooted in a sense of a user, egotism, pragmatism, alienation of man from nature, from each other, from countries, population, confessions. All these present a real threat for the mankind.

The effort to the unity on the basis of general and mutual interests, the mankind's perception of its role as a collective subject of biosphere, responsibility for the life on the planet these are the ways to create a new ecological culture able to harmonize the relations between man and nature on the base of human mind, morality and will.

Ecological culture presumes such a mode of life when the society by system of moral values, ethic principles, economic mechanisms, legal rule and social institutions can form the needs and methods of their realization which will not threaten the life on the Earth.

All variety of ecological problems without solving of which it is impossible to overcome a system ecological crisis could be converged into three great blocks.

First, a deep scientific knowledge about functioning of biosphere as a repository of life is necessary, understanding of those limits within which co-evolutionary development of system "society- nature" is possible. The theory of biotic regulation is a fundamental basis realization of which will make possible to optimize a human activity on the Earth.

Secondly, it is essential to work out legal and moral regulations, taboos which will not allow exceeding those limits. The very perception that the mankind is a single collective subject of biosphere is indispensible condition of responsibility for the biosphere fate. Altruism, ability to give up a part of the present for the sake of the future serves as a test on mental rationality of the mankind. Liability of people, social for social being, must be amplified by the responsibility of man in front of the nature. New moral philosophy, ecological ethics fairly put forward a question about the rights of the nature, restore the idea of reverence before the life.

At last, all these rules and values are called to correct the culture which stopped to fulfill its adaptive function between man and nature, to co-assist the formation of ecological culture, ecological perception of individuality and society. Translation of values of ecological culture in education, formation of ecological competence of any professional is a real ground for a social progress.

Such structure of all ecological problems contributes to integration of efforts of investigators and practical persons. Those who understand the essence of the ecological challenge are responsible for the right choice of the strategy of development, for formation of a new awareness and ecological culture without which this strategy cannot be realized.

Ecology has no borders. However every country, people are developing in the limits of their national ecosystem. The unity of landscape and ethnos, nature and economy make the national shapes of the world (G. D. Gachev), unique cultures which cannot be imported as Canadian jeans or French cosmetics. Technology in its ecological dimension is the level of harmonization of natural potential of the territory and intellectual wealth of people. Their unity is a guarantee of prosperity of every single country and the world as a whole.a new perspective is needed to guide how medicine advances and returns benefit to society. This perspective must be embedded in knowledge of changes in the natural and social worlds, and the shifting patterns of disease. Indeed, not only must health care providers and institutions reexamine their stance in the world, but all individuals and communities would do well to become aware of how their wellbeing is connected to other people, other species, and the natural world.

The health of Earth's ecosystem is the foundation of all health. Human impact in the form of population pressure, resource abuse, economic self-interest, and inappropriate technologies is rapidly degrading the environment. This impact, in turn, is creating new patterns of human and ecosystem poverty and disease. The great challenge is to integrate an ecological perspective into health care and public health practice in ways that demonstrate understanding of

the identifiable changes occurring in the natural and social worlds around us, as we collectively develop the new social contract for medicine. The tension among ecosystem health, public health, and individual health is reaching a breaking point at the beginning of the Twenty-First Century.
Ecological Medicine is a science relating to physiological, biological, genetic, socioeconomic, cultural, etc., changes now taking place in our cosmos. It is concerned with disease and health processes of several components of the living organism. Its task is to recognize, evaluate, prevent, and treat all the above variables which are in integral part of the disease process. Thus, in this way, only the mankind can be thoroughly and completely investigated as a unique psychophysiological, socioeconomic, and cultural ecologic entity.

Indicators of humoral immunity in patients with cholelithiasis after laparoscopic cholecystectomy and rehabilitation treatment

R. Shnitser, J. Peresta, S. Dzhupina, A. Kuzma, T. Pyndus, P. Dzhupa

Introduction

According to the medical and statistical research of cholelithiasis in Ukraine and worldwide, is one of the first places in the structure of gastroenterological diseases. "Gold standard" treatment of this pathology was laparoscopic cholecystectomy. However, in many patients after surgical treatment occurs so-called postcholecystectomical syndrome due to motor dysfunction of tonic gallbladder, bile ducts and sphincter. There is a need pathogenetic basis of rehabilitation treatment of cholelithiasis, including studies of the indicators of humoral immunity link.

The study

was to study the influence of rehabilitation treatment with the use of drinking mineral water "Polyana Kupil" on parameters of humoral immunity of patients with cholelithiasis after laparoscopic cholecystectomy.

Materials and methods

Assessment of humoral immunity was done 28 patients who had received hospital treatment in the surgical department number 1 OKL Uzhgorod University. A. Novak and which was conducted on laparoscopic cholecystectomy of cholelithiasis. Most patients (88%) were in the sanatorium rehabilitation treatment " Polyana " in the early period after surgical treatment (5-7 days).
Duration of disease in households ranged from 1 to 21. The clinical picture of calculous cholecystitis in these patients manifested hepatic colic attacks, 18% of patients disease run latency. Most patients identified associated gastrointestinal disorders: chronic hepatitis B - in 28%, gastric dyspepsia - 40%, dyskinesia of thick intestine - in 38%, chronic pancreatitis - 22% of patients.
During the 24-day rehab treatment recommended internally

Table 1. Immune status of patients with cholelithiasis in pre-and postoperative period after LCE and after rehabilitation treatment in the sanatorium "Polyana" (M±T).

Immunological studies	Healthy (n=24)	Before surgery (n=26)	after rehabilitation (n=26)
Humoral immunity			
Complement titer (47.0±0.5)	47.0±0.5	40.2±6.1	43.8±2.0
The level of total IgE AT (6.0 ± 0.5)	6.0±0.5	8.8±9.8	3.9±3.0
Staphylococcal antibody titer microbial (6.8±0.8)	6.8±0.8	3.6±2.8	3.6±2.0
Antibody titer tissue			
Adrenal	4.9±0.8	2.3±2.0	2.8±1.8
Hastro new to 10 cu	5.5±1.5	18.8± 11.3	11.0±7.0
Secretion new	5.2±1.0	10.2±7.3	6.6±4.6
ChCCP to 8 cu. units.	5.3±0.3	11.5±8.6	6.9±5.7
Gallbladder	5.4±0.7	6.9±7.6	5.8±6.3
Pancreas to 15 cu. units.	11.6±1.7	6.8±7.6	5.4±5.7
CIC 13.5 ± 1.5 mmol / l	13.5±1.5	25.1±13.1	22.4± 1 0.4
Ceruloplasmin 30 mg%	33.2±1.5	32.1±12.9	32.9±6.4

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heated to 38 ° C mineral water Polyana Kupil 150-200ml slowly for 40 minutes before meals 3 times a day, ginseng extract. Mode of patients was free, except the load on the muscles of the anterior abdominal wall.

Immunological studies were conducted to surgical treatment after laparoscopic cholecystectomy and after rehabilitation treatment and included the determination of these parameters: titer of total IgE, complement, the level of bacterial tissue antibodies, circulating immune complexes, ceruloplasmin. The control group comprised 24 healthy individuals.

Results and discussion

Comparison of immunological parameters for surgical treatment and after rehabilitation showed that tissue levels of antibodies hastro new, secretion new of cholecystokinin-pankreozymin, gallbladder decreased, but left more than a group of healthy subjects (Table 1). Complement titer increased, but not above normal. Were high levels of circulating immune complexes and ceruloplasmin, indicating the presence of inflammation. The level of IgE decreased in 2,3 times, testified to reduce the occurrence of immune reactions in patients with reagent type after rehabilitation.

When more detailed analysis of test protocols, we found that immunological parameters approaching to normal in patients with limited disease term (1-3 years), absence of concurrent disease of the digestive system and uncomplicated postoperative period. After rehabilitation treatment hardly changed immunological parameters in those patients who were not violated and to surgical treatment.

Conclusion

Comprehensive rehabilitation of patients with laparoscopic cholecystectomy utilities after using mineral water "Polyana", Carpathian herbs has modulating effect on the immune system of patients.

Patients with large term illness requiring more detailed examination for the presence of concurrent disease and medication after LCE. Course of the rehabilitation treatment of such patients is recommended to take in more remote terms after operation (2-4 weeks).

The prophylaxis of preoperative and early postoperative complications of the cholelithiasis patients after the performance of laparoscopic cholecystectomy

R.I. Shnitcer, Y.Y. Peresta, O.V. Ihnatenko, A.V. Turyanutcya, O.M. Kuzma

Introduction

The analysis of the data [1,2] affirm the fact that cholelithiasis is one of the most widespread diseases, which requires surgical intervention. According to different records, its rate among the population of the developed counties is 8, 0 – 15, 0 % [3]. In the course of the last decade, there appeared a tendency of growth of cholelithiasis. The number of operative interventions in connection with acute and chronic calculous cholecystitis is simultaneously growing.

The implementation of laparoscopic cholecystectomy into the wide surgical practice and also its combination with endoscopic papillotomy gives the possibility of minimally invasive treatment of calculous cholecystitis and complicated forms of cholelithiasis. This essentially improves the results of the treatment of this pathology and accelerates the time of hospitalization, social and medical rehabilitation of the patients.

In the opinion of the majority of authors, the complications, with taking into account the specifics of mistakes, which occur, while carrying out laparoscopic cholecystectomy, require painstaking research and analysis, which will give the possibility to improve the quality and results of operative interventions of the cholelithiasis patients.

Materials and methods

We have investigated the results of laparoscopic cholecystectomy, which were carried out on 242 patients with cholelithiasis during the period of 2004-2011. Men made up 7% (17 patients), women - 93% (225 patients). The age of the patients is 14-79 years. All patients up to the operative intervention had chronic calculous cholecystitis. In 98,0% of the patients cholecystectomy was performed by laparoscopic method, the rest of the cases turned to an open method of cholecystectomy. There was no special selection of patients, that is laparoscopic operations were conducted according to the same showings as open cholecystectomy. Operative interventions were conducted after a thorough examination of the patients.

The examination of cholelithiasis patients necessarily included anamnesis, general clinico-laboratorial examination, RCD of the organs of hepatobiliary zone, fibrogastroduodenoscopy, fluoroscopy of the organs of thorax, spirometry, electrocardiogram, echocardiography and the examination of the gynaecologist. This gave us the

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possibility to verify the presence of concomitant pathology and to determine the direction of the further diagnostic search. Having discovered the pathology of abdominal cavity, which required correction in a surgical way, with a prolonged differentiation of elements in the Kalo triangle, preference was shown for the open method – laparotomy.

The presence of previous operations on the organs of abdominal cavity in 12 patients, especially in the upper part of the stomach, didn't obstruct the performance of laparoscopic cholecystectomy. In such cases the spike process in the abdominal cavity was not strongly expressed and didn't create any obstacles. The change of the puncture of the stomach in order to put carboxyperitoneum on and to inject trocar, the conduct of finger revision of the abdominal allowed us to diminish the frequency of refusals of the given type of operative intervention in the presence of postoperational scars.

Typical laparoscopic cholecystectomy was performed with the help of clipsing of arteria et ductus cystica.

Intraoperative prophylaxis of laparoscopic cholecystectomy complications includes keeping up the six defined tactical approaches, depending on the type of constitution and the presence of concomitant pathology of the patients, keeping up the mechanical principles of the operation, correct choice of the mode of electric current, realization of conversion in doubtful cases.

All operations (100%) necessarily ended up with drainage of under hepatic space, which provided evacuation of scrubbing waters, blood and jaundice. There were no complications, which could be conditioned by the presence of drainage. Drainage didn't exceed the patient's stay in hospital. Drainage tubes were excreted on the second – third day from the moment of operation.

Results and discussion

Laparoscopic gall bladder removal was successful in 237 patients (98,0%) from 242 patients. In 5 (2,0%) patients we had to turn to open cholecystectomy. The reasons for this were the bleeding from the branches of bladder artery in 1 incident, solid scar inflamed infiltrate in the area of hepatoduodenal ligament in 4 cases (1,6%), which considerably obstructed the separation of the gall bladder and were accompanied by a distinct bleeding of tissues.

For the estimation of the results of laparoscopic cholecystectomy the Jannet classification has been used. In accordance with it, there are five variants of the behavior of postoperative period. The first class – operations without technical and postoperative complications - 228 (94,2%). The second class – operations with technical difficulties, which were not reflected on the behavior and duration of the postoperative period – 8 (3,3%). Among them were operations with the perforation of gall bladder – 2 (0,8%), with bleedings from art. cystica – (0,8%) of the front abdominal wall – 1 (0,4%) and the gall bladder bed – 3 (1,2%). The third class – operations, after which appeared complications, that led to the extension of the postoperative terms – 5 (2,1%). Here also belong pneumonia patients – 1 (0,4%), paroxysm of ciliary artery – 1 (0,4%), hypertonic crisis – 1 (0,4%). The fourth class – operations, after which appeared complications, which needed invasive methods of treatment – 1 (0,4%). The gathering of the gall under the liver was detected in four patients, but the mini-invasive interference under the control of ultrasound was performed only for one patient. The fifth class – lethal incidents, which were not observed in the postoperative period.

Scrupulous manipulations on the gall bladder duct and its diligent separation from the scar accretion allow the differentiation of the structure and prevention of such serious complication as the lesion of hepaticocholedochus and hepatic ducts. The separation of the gall bladder duct should start at its neck. It is possible to follow the duct till the inflow into the general bilious gall, after painstaking sceletisation.

It is necessary to be very attentive while separating the gall bladder artery, which has a lot of correlations with the gall bladder duct. Especially difficult is the search of the artery in the presence of scar-inflammatory changes of hepatic-duodenal chord. The injury of the artery is accompanied by intensive bleeding, which is endoscopically hard to stop. Similar complications we have observed in 2 cases. In one case, the bleeding has been stopped laparoscopically in the other case, we had to turn to conversion with the bandaging of the artery.

Often intensive bleedings can appear after the removal of the gall bladder from its bed. The source of such bleeding can be additional vessels, which lead to the bed, solid scar and inflammatory accretions, which don't allow to separate the bladder subserously. If the arterial vessel was seen, we clipped it with 1-2 clips, and with the diffuse inflow of blood from its bed, it can be stopped by coagulation with the application of special diathermic electrodes, hydro-thermocoagulation or bipolar coagulation. In 3 patients we observed intensive bleeding from the bed, but we succeeded to stop it laparoscopically.

While removing the gall bladder from the abdominal cavity, especially with large concrements, bleedings of the front abdominal wall can occur as a result of the accelerated strain of muscles and injury of muscular vessels. As a rule, such bleedings are diagnosed laparoscopically. It is reasonable to stop them by suturing, because after electrocoagulation there can develop necrosis of muscles with suppuration. In one patient we have observed such bleeding, which was diagnosed in the course of the operation and was stopped by suturing.

During the removal of the gall bladder its wall was perforated in two observations. The 2-3mm diameter aperture has been closed with the help of a clutch. After the aspiration of gall, which ran out and the irrigation of the under hepatic area the operation has continued. In one of two cases the prolapse of concrements was observed, which were evacuated with the help of a clutch-like clamp. Postoperative period of such patients has passed by without any complications.

The prevention of purulent complications was carried out by means of assiduous intra-operational homeostasis with the coming control and prescription of antibiotic therapy. For the latter we have used cephalosporin antibiotics – pre-venous insertion 1 hour before the operation. By the intraoperational injury of the integrity of gall bladder the insertion of antibiotics was prolonged during 3-4 days after the operation.

In the process of our work we have tried out a number of preventive measures against the inflammatory and purulent processes in the wound, through which the gall bladder was

excreted. The drainage of the wound reduces but doesn't prevent the suppuration. The irrigation of the wound by betadine solution during 1-2 minutes considerably lessens the frequency and significance of the inflammatory reaction, it almost eliminated the suppuration.

For 50 year-old patients, who were overweight, had varix dilatation of the lower limbs with thrombophlebitis of any localization (even anamnesis), cardiovascular diseases, prophylactic thromboembolie of the pulmonary artery has been conducted. For this purpose, elastic bandaging of lower limbs was used, fraxiparine (0,3 mm a day) was inserted during the stay in the hospital, with the transfer to water-soluble aspirin (with early intensification in 6-8 hours after the narcosis). This gave us the possibility to avoid thromboembolic complications of the shallow branches of the pulmonary artery. After the conducting of conservative treatment the patient was discharged on the 10-th day to the rehabilitation treatment into the health resort "Polyana". The conducting of operations by reduced carboxy pneumoperitoneum contributed to the reduction of complications of cardiovascular and respiratory system.

The reduction of complications of cardiovascular and respiratory system can be achieved by the conduction of operations by the reduced pressure of carbonic acid gas in the abdominal cavity. In 30% of cases we kept the pressure 6-8mm, in 60% - 8-10mm, and only in 10% - up to 12mm. This allowed to avoid manifestations of decompensation of this systems in the last 3 years.

Complex prophylaxis of complication of respiratory organs has been conducted for elderly and patients with concomitant pathology.

The duration of the laparoscopic cholecystectomy operation of cholelithiasis patients continued average 42,3+-3,8 minutes (from 25 to 95 min). The investigated index largely depended on the significance of pathomorphological changes of the gall bladder and surrounding tissues. This factor was exactly the cause of the intraoperational complications in 8 (3,3%) patients. The conversion on traditional cholecystectomy was carried out in 3 (1,2) operated patients. The duration of the postoperative period in cholelithiasis patients, who has undergone laparoscopic cholecystectomy comprised 3,0 +- 1,2 days. Uncomplicated postoperative period was registered in 235 patients and they were discharged in the term from 3 to 5 days after laparoscopic cholecystectomy. Early postoperative complications have developed in 7 patients. Short-term temperature rising in the term from 2 to 4 days has been noticed in the postoperative period in 8 cases. In two of them during ultrasound examination of hepatobiliar zone temperate accumulation of liquid in the under liver area was detected. The state and the records of ultrasound examination turned back to normal in 1 patient after the antibiotic therapy. In one patient the accumulation of gall in the under hepatic area was evacuated with the help of 2 séances of punctual aspirational interference under the control of residual-current device. In 2 patients of elderly age (72 and 75 years) with difficult cardiovascular pathology, complications have developed (paroxysm of ciliary arrhythmia and hypertonic crisis). Patients were discharged after the removing of drainage, normalization of temperature. No lethal cases have been observed.

Conclusions

So, the frequency of development of complications of laparoscopic cholecystectomy depends on the level of professional preparation of the surgeon and his assistant, on the degree of significance of morphologic changes in the area of the operation, on the ability to correctly estimate the clinical situation. Diligent analysis of even the smallest complications and mistakes during the operative interference allows to prevent the in the future.

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The system of complex control of human fitness under application of ozone therapy when treating different diseases

A.N. Serova, M.A.Kurbatov, G.A.Boyarinov, I.G.Tsigankova

The basis of the method is the information technology of analysis of biorhythmological processes of human – fractal neurodynamics (Smirnov YU. A., 2001). To get the necessary information it is sufficient to register ECG in any standard lead during 5 minutes.

This method allows: in the mode of screening, to determine the level and reserve of cardiovascular system, vegetative and central regulation, and also to estimate the deviation of these indices, to estimate the level of compensation and energy resources of the organism at different levels of regulation, to determine the ability of self-regulation in the mode of biological feedback, to estimate and prognose psychophysical state of the patient, to control functional state of a patient and to estimate the effectiveness of different methods of therapy during conduction of treatment-and- prevention work; to make complex medical report and to give necessary recommendations.

The research has been conducted before and after the introduction of ozonized solution in concentration 2 mg/l to 78 patients.

It has been shown for certain significant possibility to control the indices of functional state of patients, to prognose their changes, to estimate the resources of organism and determine the effectiveness of treatment.

The aim of research

to exercise quality control of the effectiveness of intravenous injection of ozonized physiological solution for human organism fitness under different diseases when using hardware-software complex "OMEGA-M" designed for the analyses of the biorhythms separated from EKG in the wide strip of frequencies by the newest information technology of biorhythm analyses «fractus neirodinamic».

Materials and methods

The standard examination of 78 patients in the age of 23 – 74 (38 men, 40 women) with different diseases has been carried out, and in the treatment the ozonized physiological solution in the concentration 2 mg/l has been used.

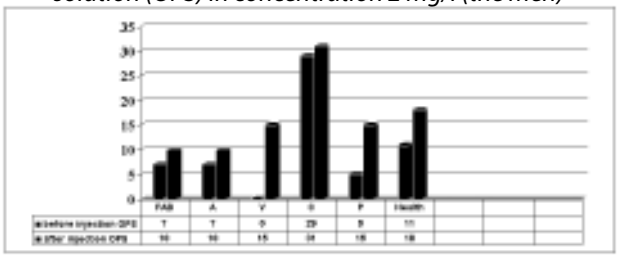
The intravenous infusion of 200 ml 0,9% ozonized physiological solution with concentration of ozone 2 mg/l has been daily conducted to the patients during 15 – 20 minutes. The course of treatment – 10 procedures. The research before and after the injection of ozonized physiological solution has been done by complex "Omega-M":

1. estimation of state of cardiovascular system and neurohumoral regulation according to "golden section" of time parameters of EKG;
2. estimation of indices of vegetative regulation by methods of static, temporal and spectrum analysis of heart rate;
3. estimation of state of central regulation and state of endocrine system by method of neurodynamic analysis of human biorhythms;
4. estimation of psychophysical state of the patient by method of phase analysis and mapping of cerebral biorhythms;
5. estimation of the system of harmonization of human biorhythms and determination of information index of immune status by method of fractal analysis;
6. generation of complex medical decision according to the results of computer analysis, documentation and printing of the results of the research

Dr.Alla N. Serova

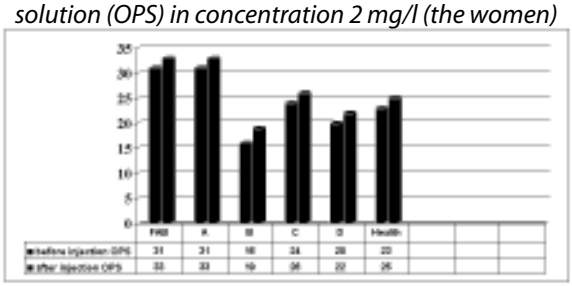
The men showed stable increase of all investigated indices:

Diagram 1. Change in the state of functional indices of patients before and after intravenous injection of ozonized physiological solution (OPS) in concentration 2 mg/l (the men)



A - adaptation layer of cardiovascular system in the range of – 7 – 10%,
V - vegetative regulation in the range of – 0 – 15%,
C - central regulation in the range of – 29 – 31%,
P - psychoemotional state in the range of – 5-15%,
Healf - integral index of state of the patient in the range of – 11-18%,
FAB - all indices in whole in the range of – 7-10%.

Diagram 2. Change in the state of functional indices of patients before and after intravenous injection of ozonized physiological solution (OPS) in concentration 2 mg/l (the women)



The women also showed stable increase of all investigated indices:
A -adaptation layer of cardiovascular system in the range of – 31 – 33%,
V - vegetative regulation in the range of – 16 – 19%,
C - central regulation in the range of – 24 – 26%,
P - psychoemotional state in the range of – 20-22%,

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Health - integral index of state of the patient in the range of – 23-25%,
FAB - all indices in whole in the range of – 31-33%.

Conclusions:

1. The system of complex computer examination of human fitness "Omega-M" gives an opportunity to control the effectiveness of application of ozonized solutions in treatment of different diseases;
2. "Omega-M" allows to prognose the dynamics of human fitness;
3. It allows to estimate human reserve with numeric accuracy;
4. It allows to detect the abilities of self-regulation in biological feedback,
5. "Omega-M" can be recommended to doctors of all specialities for carrying out quality control of the treatment.

The genital structural features of the urinary bladder gland apparatus of people in different age

Vagif Shadlinskiy, Gjulkyz Huseynova

Macro-microscopy and morphometry methods have studied glands sphincters on total preparations of a urinary bladder received from 54 corpses of people of different age (from newborn till the senile period), without a pathology of bodies to device urine-genital. The glands were investigated with the application of stereomicroscopic-binocular microscope MBS-9. For reception of micro preparations cuts of the different zones of a bladder in the thickness 5-7 microns, painted whith hemathoxylin-eosin, azure-2-eosin and by hemathoxylin – picrofucsin on Van – Gizon. In the stages of the maturity and teenage age the parameters of the measure and quantity of the urinary bladder glands in the women has different from men, s. data of field distinction it is especially characteristic for reproductive age of postnatal ontogenesis. The genital dimensional features of glands are defined under the relation of length, width and the areas of initial departments.
Keywords: genital features, gland, urinary bladder

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Introduction

The general principle of the macro microscopic structural organization of walls small glands of a hollow internal has been studied of some authors [4,5,9]. At the same time, a bladder, carrying out the major physiological role often is exposed to various traumas [8] and to pathologies. Epithelium mucous membranes can be a development basic point adenocarsinomas, adenomas, other pathology, not only life worsening quality, but also a being straight line for it threat [1,2] that allows to consider research of their structure in norm as an important problem of modern anatomy.The knowledge of the micro organization and quantity parameters of glands of a mucous membrane of this organs in norm is important and as a standard material for pathologists for the analysis a biopsy material. However, the method of macro-microscopy allowing on a considerable extent of a wall of organ to investigate its gland, preliminary painted methylene dark blue [6], in relation to a urinary bladder is unfairly ignored. Therefore now there is no data about anatomy, topography and quantity parameters of these organs glands, especially, about their sexual structural features. The data available in the literature concerning anatomy and topography of a urinary bladder glands is sketchy, fragmentary, deprived quantitative gradation or these works are executed for a long time, or on pathologically changed, insignificant material in the quantitative plan [7], or the data is received in passing, at studying lymphoid structures and are deprived also detailed and detailed information [1]. As to genital features of a structure of urinary bladder walls glands, anybody didn't investigate them earlier.

Research objective

was studying of genital features of a urinary bladder glands of people in different age.

Research material and methods.

Glands of a urinary bladder walls are studied at people men

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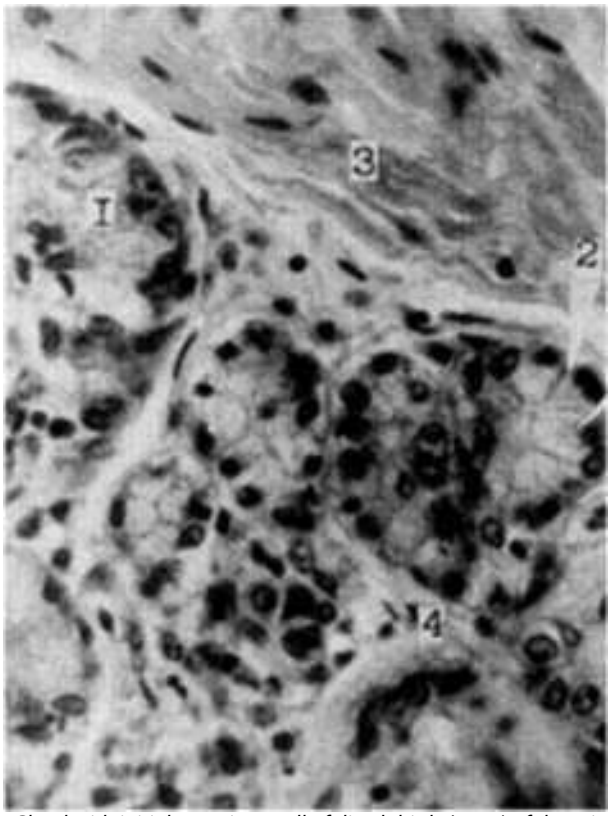


Fig. Gland with initial parts in a wall of distal thirds (parts) of the urinary bladder at the boy of 19 years. A micropreparation. 1-initial part of gland; 2-glandulosit; 3-mucous membrane; 4-connector tissue structures between initial parts. Coloring by hematoxylin-eosin, lcr.460 x.

and female, died or victims from the casual reasons which did not have pathologies of the urinogenital device. By a method of macro-microscopy of gland (on R.D.Sinelnikov) have been investigated on total urinary bladder preparations (in different sites of its wall - proximal – top, average and distal - bottom thirds of bladder) in the different age periods. The investigated material is subdivided into groups, according to the standard scheme of an age per iodization [3]: at newborns (6 boys, 5 girls), at early children's age (5 boys, 5 girls), at teenagers (5 boys, 4 girls), in 1st period of mature age (6 men, 6 women) and at senile age (6 men, 5 women). The cause of death of people was defined on the basis of the path-anatomical diagnosis and the conclusion of medico-legal opening of corpses of people. A material for research examinations in different departments association "Medico-legal and pathological anatomy" Ministry of Health of Azerbaijan Republic, not later than 18 hours after death collected. At macro-microscopic studying of total organ preparations, the separated urinary bladder were washed out in a bathroom with water; after that a studied material placed in a glass jar, filled with a solution of 0,5 % of acetic acid from painting gland 0,05 % a solution methylene dark blue [6]. Coloring spent at room temperature within 24-36 hours. Coloring considered finished when from a bladder mucous membrane with the help frontal loupe was accurately defined the small glands, looking like dark anatomic formations. Throughout 12 hours a urinary bladder preparation fixed in the sated solution an acid ammonium - molybdenum. At carrying out of macro - microscopic researches used stereomicroscope MBC-9 (oc. 8; ob. from 0,6 to 8), defined forms of glands and counted up total, density of their arrangement (at use eyepiece grids) with the subsequent recalculation of glands quantity having on the area of 1 sm^2 of a organ wall. For reception of histological micro-preparations 1, 0 x 0, 5 sm fixed slices of different parts of a bladder in the sizes mainly in 10 % neutral formalin (in need of a Karnua liquid). Longitudinal histological cuts, thickness 5-7 microns, painted whith hemathoxylin-eosin, azure-2-eosin and by hemathoxylin – picrofucsin on Van – Gizon. Counted up some dimensional parameters (length and width) glands initial department (with the help oculyar rulers, mm).

Morphomethrical data processing included calculation of arithmetic-mean indicators, their errors; reliability of distinctions was estimated by a method of confidential intervals.

Results of researches and their discussion.

Under our data, urinary bladder glands without dependence from age and sex settle down on all extent in this organ wall. Glands have accurate contours. They can settle down is concentrated, "sating" with itself a mucous membrane when between glands there are small intervals, smaller in the sizes (fig). Initial department of gland can lie down and non-uniformly. Last variant of the organization of the glands apparatus is most typical for people of senile age. Departments (from one to four and more) are located in thickness of a mucous membrane, extracted duct channels follow, forming bends, to a mucous membrane surface, opening roundish or oval crack as between its folds, and is direct on folds.

At all investigated age groups in the whole urinary bladder genital features of quantity of glands initial department are studied. The found out distinction in this respect were absent at newborn children, at early children's age. As, by comparison of quantity of initial parts of initial department of glands at

Age, sex	n	The quantity of initial parts; bladder department			
		Proximal part	Middle part	Distal part	Unbroken organ
Newborn men	5	8,0+1,3 6-12	10,5+0,9 9-13	12,9+1,5 8-14	10,5+1,7 7-15
Newborn women	4	8,4+1,1 7-11	10,9+1,4 8-13	12,1+1,1 9-13	10,5+1,9 7-14
Early childrens age men	4	12,4+2,5 9-18	16,4+2,5 12-21	22,6+2,8 16-26	17,1+3,0 10-21
Early childrens age women	4	12,8+2,2 8-16	16,4+2,8 11-21	22,2+1,7 18-24	17,1+3,4 9-21
Teenage period men	4	15,8+2,5 13-22	19,0+3,1 16-27	24,0+3,9 21-35	19,6+2,8 15-25
Teenage period women	4	20,0+3,4 18-30	25,6+3,1 24-35	37,0+1,4 34-39	27,5+3,1 23-34
I stage of maturity age - men	6	17,0+1,1 13-21	20,0+2,3 17-34	32,0+1,6 24-36	23,0+1,6 17-29
I stage of maturity age - women	5	27,0+3,0 18-32	32,4+3,0 26-40	45,4+3,2 34-49	34,9+2,8 27-40
Senile age men	6	13,8+1,2 9-19	18,2+3,0 7-30	19,0+2,8 7-28	17,0+2,0 9-24
Senile age women	5	14,2+2,8 7-20	17,8+4,1 9-28	19,0+4,1 7-26	17,0+3,8 7-25

Table 1.Genital features of quantity of initial parts of the initial department of urinary bladder glands (on a longitudinal cut) at people of different age. The note: n - quantity of supervision; X+Sx* - arithmetic-mean calculation; min-max* - a confidential interval; p * - statistically authentic of the confidential interval.*

Age, sex	n	The area of initial department (10 mm²); bladder department			
		Proximal part	Middle part	Distal part	Unbroken organ
Newborn men	5	37,4+ 3,3 30,0-45,4	42,0+ 2,6 36,0-48,2	46,2+ 1,0 44,2-49,0	41,9+ 2,6 36,0-48,2
Newborn women	4	37,4+ 3,9 30,2-44,3	44,0+ 1,9 38,0-50,2	46,2+ 2,4 43,3-52,1	42,5+ 4,5 36,3-52,4
Early childrens age men	4	44,2+ 4,6 38,1-54,5	50,0+5,1 38,7-56,7	56,1+4,8 45,4-62,6	50,1+5,1 38,5-56,8
Early childrens age women	4	44,6+3,1 38,9-50,1	50,4+4,1 39,5-54,3	56,1+4,9 42,2-59,9	50,3+3,4 42,2-54,4
Teenage period men	4	48,6+3,1 43,5-54,4	60,2+4,1 54,6-69,5	68,2+4,4 54,6-70,4	59,0+5,8 48,6-69,5
Teenage period women	4	68,0+5,1 52,2-70,4	68,6+3,1 66,6-77,7	96,2+8,9 68,5-100,4	77,6+6,2 66,6-88,9
I stage of maturity age men	6	60,0+1,2 56,5-65,6	79,2+2,7 66,9-87,2	88,2+3,6 64,7-92,0	75,8+2,7 66,7-87,2
I stage of maturity age women	5	80,4+5,4 62,2-87,5	96,6+4,2 84,4-103,9	118,8+6,9 91,0-123,0	98,6+3,9 85,2-103,5
Senile age men	6	54,6+5,1 34,2-72,8	64,2+5,8 50,2-94,0	70,0+4,6 54,0-89,2	62,9+6,4 50,0-98,2
Senile age women	5	54,2+8,3 34,0-73,0	64,2+9,3 50,2-98,4	70,4+9,0 58,0-100,4	62,9+9,4 50,0-98,2

Table 2. Genital features of area of initial department of urinary bladder glands (on a longitudinal cut) at people of different age. The note: n - quantity of supervision; X+Sx* - arithmetic-mean calculation; min-max* - a confidential interval; p * - statistically authentic of the confidential interval.*

the whole bladder (on a longitudinal cut) at different genital persons, in the specified age periods, we reveal some features (table 1). Quantities of initial parts at newborns of a different floor don't differ, but at teenage age girls more than at boys (in 1,3-1,4 times - p <0,05), hence, at women of 1st period of mature age have more, in comparison with men in 1,2-1,3 times (p <0,05).

Similarly area of initial department on a cut at girls of teenagers throughout a wall of the whole bladder is more, in comparison with boys (in 1,3-1,5 times - p <0,05), at women of 1st period of mature age – in 1,4-1,6 times (p <0,05) more than at men (table 2).

It is necessary to notice that at all investigated age groups not only in the whole organ, but also in different parts of a urinary bladder wall genital features of the area and quantity of initial department of glands are studied. The found out distinction in this respect were absent at newborn children and at early children's age. In 1st period of mature age in walls of a proximal third (proximal part) of urinary bladder the given parameter at a women more than at men in 1,3 times (p <0,05), in its average third (middle part) – in 1,2 times, in distal thirds (distal part) – in 1,3 times - p <0,05 (table 1,2).

Studied us in all investigated age groups postnatal ontogenesis, in micro-preparations of the whole bladder define genital features of some dimensional parameters - lengths and width of initial department of glands. The found out distinction in this respect too were absent at newborn children and at early children's age. The length of initial department throughout a urinary bladder wall at teenage age at girls in 1,1-1,4 times more than at boys, and in 1st period of mature age – in 1,2-1,4 times is more at women, in comparison with men (diagrams 1). As to other parameters of glands, i.e. width of their initial department it throughout a wall of a urinary bladder at girls of teenagers in 1,1-1,3 times is more, in comparison with boys, and at women of 1st period of mature age – in 1,1-1,5 times more than with men (diagrams 2).

Diagram 1Length of initial department of glands

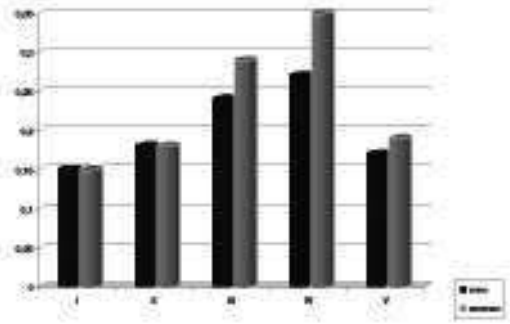
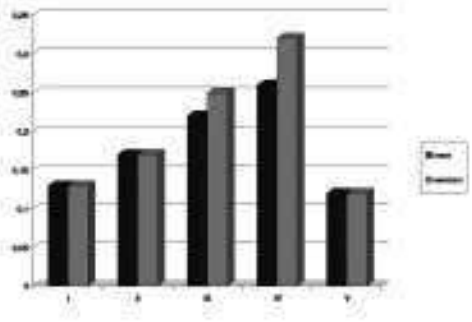


Diagram 2 Width of initial department of glands



Discussion.

The general principle of the macro-microscopic structural organization of urinary bladder glands corresponds with property of small glands of walls of a hollow internal [4,5,9]. Glands, under our data, always are present on all organ walls. Our data contradicts the opinion which is present at the scientific literature [7] a little. According to this information, «glands aren't constant formations»; but completely we divide to opinion of the specified author that «the basic areas of an arrangement of glands in a bladder wall are neck area, a bladder bottom, its triangle».

For the first time the field distinctions of a urinary bladder glands revealed by us are partly authentic, sometimes have the tendency form that, probably, is connected with rather small sizes of sample (quantity of supervision). At the same time, these distinctions have the unidirectional character specifying in prevalence of measure-quantity parameters of glands at a women, in comparison with men. The fact is interesting that from the studied five age groups these features are revealed by us in teenage and 1st period of mature age, but are absent at children and at senile age. Probably, it is connected with trophy effect of an estrogen, characteristic in the reproductive period, thanks to functional features ovary.

It is necessary to notice that field features are absent on the majority of structural indicators of glands, that is on quantity of initial departments, under the form of initial departments, and as on percentage of a parenchyma and strome at initial department of glands.

Conclusions

For the first time following genital features of a urinary bladder glands apparatus structure of the person in the different age periods postnatal ontogenesis are revealed:

1. At macro-microscopy of urinary bladder glands of the person aren't genital dimensional features of glands under the relation of quantity and the area of initial departments.
2. At histological research of urinary bladder glands are marked genital dimensional features under the relation of length and width of initial parts forming them.
3. The data of field distinction it is especially characteristic for reproductive age (in teenage and 1st period of mature age) of postnatal ontogenesis.
4. Field dimensional features are absent on the majority of structural indicators of glands (quantity of initial departments at gland, the form of initial departments, percentage of a parenchyma and strome at initial department).

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Ultrastructure alveolocytes ii type of easy rats after sharp physical activity

Vagif Shadlinskiy, Tarana Sultanova, Agasamid Isayev

One of key positions of modern medicine is the problem of mutual relations of system of breath and blood circulation in an organism. Function of lungs as special depot of blood, it is included in blood circulation system between the right and left half of heart, all-important and specialized. Besides, lungs are powerful receptor a field of the interfaced reflexes on cardiovascular system. Considering the above-stated have set for itself a problem to study a condition alveolocytes II type of easy rats at sharp physical activity.

Experiment is executed on 20 white not purebred rats-males in weight of a body 150,0-180,0 gram, which were exposed to sharp physical activity – run in rotating tredban within 2-3 hours, frequency of rotation of 19 round/minute .

During work the electron-microscopic method of research has been used. Results of research have shown that both on survey electron-gram, and at the big increases in alveolocytes II type the considerable changes caused by an ischemia of a pulmonary fabric owing to vasoconstriction, and consequently, reduction of a food of alveoluses are found out. A food of alveoluses is carried out by the same capillaries which serve for gas exchange. Fall of diffusion of oxygen after a hypostasis and a thickening aero-hematic a barrier leads to an ischemia of a parenchyma and decrease in formation of the substance produced alveolocytes of II type – surphactant.

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Production reduction surphactant at insufficient blood supply of alveoluses conducts to inhibition of metabolic processes in cellular elements, namely, in the big alveolar cages, a consequence of thatis deficiency surphactant, its washing away in a gleam of an alveolus and atelectas. In control samples, according to elektronno-histochemical

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reaction, the product of interaction with colloidal iron is defined in the form of a layer on a surface of alveoluses. As shown, increase of capillary permeability is accompanied by an exit in a gleam of alveoluses of plasma which, cooperating with surphactant,, leads to its inactivation and fall of alveoluses that even more reduces a pulmonary blood-groove, closing a vicious circle.

Thus, results research have shown that ultrastructure studying alveolocytes II type of lungs in the conditions of physical activity has not only theoretical, but also practical value for modern medicine.

Anesthesia for "duodenal mass" that appeared to be pheochromocytoma

Michael Shulman, Rao Sarojini, Tjagaraj Kalpana

Introduction:

Pheochromocytoma is a catecholamine secreting tumor, diagnosed in 1of 1000 hypertension patients with 25-50% of deaths due to this disorder that occur during the induction of anesthesia or during operations for other reasons.

Aim: Anesthesiologist awareness possible pheochromocytoma in the case of severe intraoperative hypertension.

Case Report:

Patient was a 70 years old female with recently diagnosed hypertention which was poorly controlled and history of recent abdominal pain, nausea and vomiting with duodenal mass as of radiology reading of her abdominal CT Scan. The patient was scheduled for elective Whipple operation with vascular surgery on send by due to close proximity of the mass to the IVC.

Preop physical examination was unremarkable with only exception of elevated BP 180/82 HR 70.

The patient was taken to the OR , A.line was placed before induction and R IJ cordis was placed after induction for anticipated massive blood loss/ potencial for massive blood products transfusions.

The patient had smooth induction with Versed/Fentanyl/ Propofol /Vecuronium with subsequent SBP fluctuations ranging from 100/ to 150/ and the Heart rate 60's to 70's with Sevoflurane as an anesthetic agent.

About 30 min after incision whenthe surgeons were manipulating area around duodenum trying to locate the mass the BP rose very rapidly to the level of 200/102. Increased analgesia, Propofol , anesthetic gas and Lopressor would not adequately resolve theis hypertensive episode. At that point we started to suspect another source of catecholamines, rather then pain or light anesthesia(BIS monitor showed 46-50 at that time) and we asked surgical team to stop and reevaluate the field. Almost immediately after the pause in manipulation of the affected area the BP returned to base line of 130/ and the surgeons located ball-shaped mass close to the upper pole of the right kidney.

Dr. Michael Shulman, MD

Soon after the specimen was removed form the surgical field BP was stabilized around 110/60 and HR of 60. The patient remained stable for the rest of the case and was safely extubated and transferred to the recovery room.

Pathology report confirmed the diagnosis of Pheochromocytoma.

Discussion:

Communication is critical for the patient benefit

Rapid recognition of differential diagnoses for intraoperative hypertention is very important.

Things to avoid intraoperatively in the case of Pheochromocytoma:

Sympathetic nervous system stimulants
- ephedrine
- ketamine
- hypoventilation

Agents potentiating catecholamine dysrhythmias
- Halotane

Inhibitors of parasympathetic nervous system
- pancuronium

Histamine release caused by
- atracurium
- morhpine sulphate

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Der Einfluss der Mikroflora verschiedener Biotopen der Schwangeren auf die Darm-mikrobiozönose der Neugeborenen.

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Es ist bekannt, das für die Bildung einer normalen Darm-Mikrobiozönose beim neugeborenen Kind der Gesundheitszustand und die Mikroflora der Mutter von großer Bedeutung sind. Unter heutigen Bedingungen, wenn eine nomale Zönose der Vagina eher selten wird, gewinnt die Untersuchung dieser Beeinflussung noch mehr an Bedeutung.

Vorherrschende Rolle spielt die Mikroflora des Magen-Darm-Traktes (MDT) und des urogenitaler Traktes.

Besonders vielfältig ist der Artenbestand von Mikroorganismen im MDT. Dabei unterscheiden sich die Mikro Bildung einer normalen Darm-Mikrobiozönose verschiedener Abschnitte des Verdauungskanals nach qualitativen sowie nach quantitativen Merkmalen und nach Habitaten grundsätzlich voneinander. [2] Ausserdem befindet sich die Mikroflora des MDT im permanenten dynamischen Gleichgewicht mit verschiedenen Faktoren der Umwelt, des eigenen Organismus und der natürlichen Resistenz. [10]

Die gesamte Mikroflora des Darms wird aufgeteilt in die obligate - vorherschennde Mikroflora (Bifidobakterien, Lactobakterien, Bakteroiden, Kolibakterien, Veillonella, Peptokokken, Fusobakterien und a.); die fakultative – bedingt-pathogene und saprophytische Mikroflora (Staphyllokokken, Pilze und a.); die transitorische Mikroflora - zufällige Mikroorganismen (Klebsiellen, Protea, Streptokokken, Clostridien und a.). [10]

Ungeachtet der beeindruckenden Artenvielfalt von Mikroorganismen bilden nur wenige davon die Gruppe der dominierenden Vertreter der obligaten Mikroflora, die die fakultative Mikroflora zahlenmäßig hundertfach übersteigen.

Die Mikroflora des urogenitalen Traktes bei Frauen hat ebenfalls ihre dominierenden Vertreter.

Die vorherrschenden Mikroorganismen sind L.acidophylus und L.fermentum.

Bei gesunden Frauen sind die Lactobazillen nicht nur in der Vagina, sondern auch in distalen Bereichen der Urethra dominierend, wo sie den Harntrakt vor uropathogenen Bakterien schützen.

Normalerweise entfallen nur 2-10% der gesamten Mikroflora der Vagina auf andere Mikroorganismen, von denen es bei einer Frau über 20 Arten geben kann. Zu ihren besonders oft isolierten Vertretern gehören obligate und fakultative anaeroben Bakterien: Bifidobakterien, Peptostreptokokken, Bakteroiden, Gardnerellen, Corynebakterien, Streptokokken, Pilze der Gattung Candida, Clostridien - sporenbildende Anaeroben.

Die qualitative und quantitative Zusammensetzung der Mikroflora der Vagina verändert sich während der Schwangerschaft und nach der Entbindung.

Zu Beginn der Schwangerschaft ist ein eventueller Rückgang von Lactobazillen und die Erhöhung der Konzentration von Bifidobakterien oder Kokken und Eubakterien möglich, was mit der immunsuppressiven Wirkung der Schwangerschaft auf Organismus einer Frau erklärt wird.

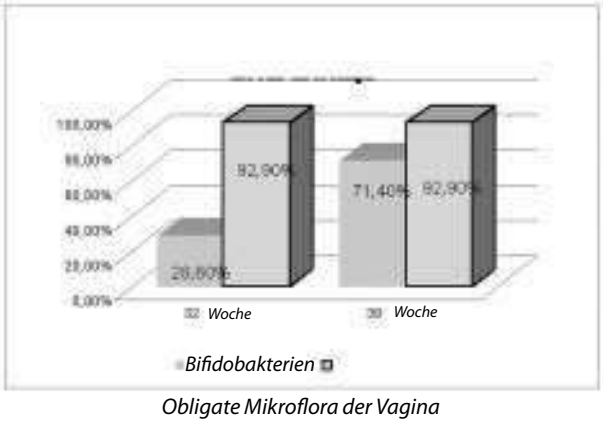
Ab 22. Woche und bis zum Ende der Schwangerschaft dominieren die Lactobazillen, es werden häufiger die Pilze der Gattung Candida isoliert, was mit der Veränderung des hormonalem (Estrogen) Hintergrundes der Schwangeren verbunden ist. [2]

Es besteht eine stereotype Vorstellung, dass die Bildung der Mikrobiozönose beim Neugeborenen während der Geburt mit der Kolonisierung seiner Schleimhäute und der Haut mit Bakterien der intestinalen, vaginalen und der Haut-Mikroflora der Mutter beginnt. [3, 4, 5]

Neben der klassischen Theorie der Besiedlung von wichtigsten ökologischen Nischen des neugeborenen Kindes mit Mikroorganismen, während es durch den Geburtskanal der Mutter kommt, ist eine andere Ansicht entstanden, dass eine normale Darm-Mikroflora beim Fötus in der zweiten Hälfte der Schwangerschaft dank dem Phänomen der bakteriellen Translokation von der Mutter zustande kommt. Der Inhalt der Erscheinung der bakteriellen Translokation besteht darin, dass bakterielle Vollzellen die epitheliale Barriere überwinden und in die regionaren mesenteralen Lymphknoten gelangen. Das weitere Schicksal dieser Zellen hängt vom Verhältnis der Intensität des Prozesses des Bakterieneindrangs und des Immune Responce: entweder werden die Bakterien durch Makrophagen der mesenteralen Knoten aufgelöst (Lysis), oder sie gelangen durch die Pfortader in die Lebersinus. Falls die Makrophagen der Leber die eingedrungenen Bakterien nicht zu unterdrücken vermögen, können die letzten im Blutsystem auftauchen [1].

In diesem Zusammenhang entsteht die Notwendigkeit des bakteriologischen Monitoring und der Korrektion von dysbiotischen Störungen bei einer schwangeren Frau zur Bildung einer normalen Mikrobiozönose beim Kind.

Das Ziel dieser Forschungsarbeit bestand in der Untersuchung des Zustandes der Mikrobiozönose der Genitalien bei schwangeren Frauen und deren Wechselbeziehung mit der Dickdarm-Mikroflora und dem Schleim in Nase und Rachen von Neugeborenen.



Obligate Mikroflora der Vagina

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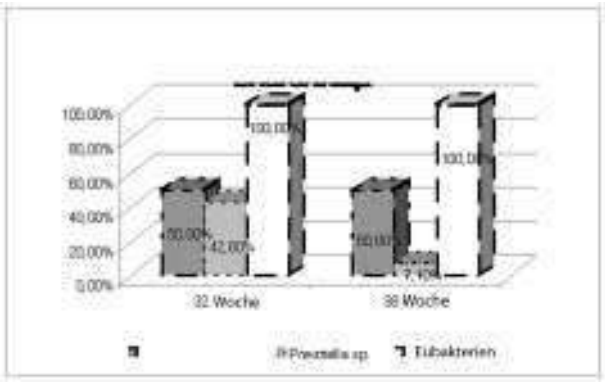
In der Beratungsstelle und im Entbindungsheim Nr. 5 wurde eine klinisch-bakteriologische Untersuchung der schwangeren Frauen in der 32. und 38. Schwangerschaftswoche sowie der Neugeborenen in den ersten Lebenstagen durchgeführt. Bei allen Schwangeren erfolgte eine bakteriologische Untersuchung der Exkremente und der Vagina, bei Neugeborenen wurde der Schleim in Nase und Rachen bei der Geburt und die Exkremente am 5. Tag nach der Geburt untersucht. Die Untersuchung des Mikrobenbestandes des Dickdarms und der Vagina und die Bewertung seiner Störungsschwere wurden nach jeweiligen Empfehlungen. durchgeführt [6, 7, 8]. Bakteriologische Untersuchung des Schleims in Nase und Rachen erfolgte unter Anwendung einer erweiterten Nährböden-Palette zur Kultivierung von aeroben und anaeroben Mikroorganismen.

Bei der bakteriologischen Untersuchung der Vagina wurden bei allen untersuchten Frauen ausgeprägte dysbiotischen Störungen aufgedeckt. Die Bifidobakterien fehlten in 71,4% der Fälle in der 32. Woche, jedoch ging dieser Kennwert in der 38. Woche bis 28,6% zurück.



Fakultative Mikroflora der Vagina

Die nun fällige Schlussfolgerung lautet, dass selbst beim klinisch normalen Verlauf der Schwangerschaft die Durchführung einer bakteriologischen Untersuchung der Mikroflora der Vagina mit deren anschliessenden Korrektion erforderlich ist.

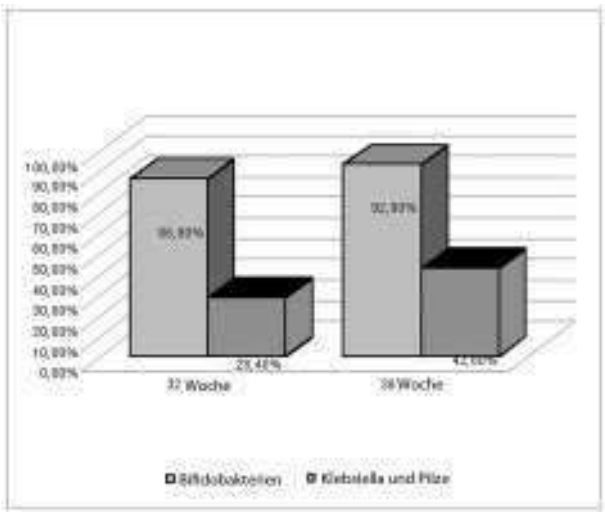
Die Lactobakterien konnten in der 32. und 38. Woche bei 7,1% der Schwangeren nicht isoliert werden.

Unter den Vertretern der fakultativen Mikroflora wurden in 50% der Fälle in der 32. und 38. Woche grössere Mengen von Peptostreptokokken isoliert. Prevotella sp. wurden bei 42,8% in der 32. Woche (10^6 CFU/ml) und bei einer schwangeren Frau (7,1%) in der 38. Woche registriert.

Die Eubakterien waren in der Vagina bei 100% der Schwangeren in der 32. (10^5 CFU/ml) und in der 38. Woche (10^6 CFU/ml) präsent.

Der Fachliteratur zufolge spielt Prevotella (Bakteroiden) eine vorherrschende Rolle bei der Entstehung von Komplikationen während der Post-OP-Behandlung. Durch die Vermehrung der obligaten Flora wird die fakultative Flora unterdrückt. Ihre Konzentration geht signifikant zurück.

Bei den Schwangeren in der 32. und 38. Woche waren die Störungen der Darm-Mikroflora mässig ausgeprägt und entsprachen der Darm-Dysbakteriosestufe 1-2. Das Ungleichgewicht der obligaten Mikroflora zeichnete sich hauptsächlich durch einen unbedeutenden Rückgang der Zahl von Bifidobakterien bei jeweils 14,2% und 7,1% der untersuchten Personen aus. Die Kolibakterien wurden in

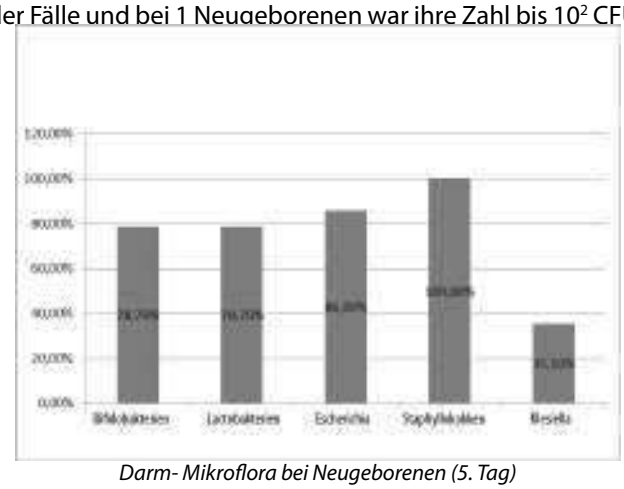


Darm-Mikroflora bei schwangeren Frauen

formal normalen Zahlen Isoliert. Die bedingt-pathogenen Bakterien, die zur fakultativen Mikroflora gehören, wurden in diagnostisch signifikanten Zahlen bei 4 Frauen in der 32. Woche (Zunahme von klebsiella und hefeähnlichen Pilzen der Gattung Candida in je 2 Fällen), bei 6 Frauen in der 38. Woche (Zunahme von klebsiella - 4 Fälle, und hefeähnlichen Pilzen der Gattung Candida - 2 Fälle) entdeckt. In der 32. Schwangerschaftswoche wurde die Zunahme der Zahl der Vertreter der fakultativen Mikroflora von keinen Veränderungen seitens der obligaten Mikroflora begleitet. in der 32. Woche wurde die Zunahme der Zahl von Klebsiella (10^7 CFU/ml) nur in 1 Fall vom Rückgang von Bifidobakterien (10^2 CFU/ml) und Lactobakterien (10^4 CFU/ml) begleitet. Die mikroökologischen Störungen im Dickdarm verliefen in allen Fällen symptomlos.

Die gewonnenen Ergebnisse bezüglich der Darm-Flora sind weniger informativ, weshalb, nach meiner Meinung, statt planmässiger Untersuchungen der Magen-Darm-Flora die Durchführung einer bakteriologischen Untersuchung der vaginalen Flora als zweckmässig erscheint. Die Zahlen von klebsiella und Pilzen in den Exkrementen der Schwangeren überstiegen nicht die zulässigen Konzentration.

Bei der bakteriologischen Untersuchung von Exkrementen der Neugeborenen fehlten die Bifidobakterien nur in 14,2% der Fälle und bei 1 Neugeborenen war ihre Zahl bis 10^2 CFU/



Darm- Mikroflora bei Neugeborenen (5. Tag)

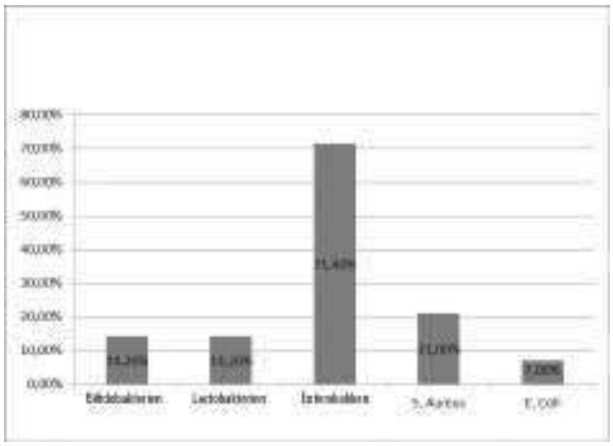
ml zurückgegangen, in anderen Fällen konnten sie in formal normalen Mengen isoliert werden. Die Veränderung der Zahl von Lactobakterien war ebenfalls unbedeutend: sie fehlten bei 1 Neugeborenen und waren bei 2 Neugeborenen bis 10^3 CFU/ml reduziert. Eschrichia fehlten bei 2 Neugeborenen.

Bei allen Neugeborenen wurden aus Exkrementen die Enterokokken isoliert, deren Zahl den Normwerten entsprach. Mehr ausgeprägte Veränderungen beobachtete man seitens der fakultativen Mikroflora: bei allen Neugeborenen wurden Staphyllokokken (10^3 – 10^7 CFU/ml), und in 1 Fall - S.aureus isoliert.

In 5 Fällen wurden aus Exkrementen Klebsiella (10^7 – 10^{10} CFU/ml) isoliert/. Es sei darauf hingewiesen, dass in 3 Fällen identische Stämme von Klebsiella aus Exkrementen der Schwangeren in der 38. Woche isoliert wurden.

Bei 2 Neugeborenen wurde in den Exkrementen Enterobacter aeroigenes (10^9 CFU/ml) registriert.

Die Analyse der Zusammensetzung der Darm-Mikroflora des Neugeborenen am 5. Tag zeigte, dass der Mikrobenbestand den Normwerten der Mikroflora eines einjährigen Kindes entsprach. Nach meiner Meinung, ist dies durch die Gesundheit der untersuchten Frauen, normale Zönose der Vagina bei 38. Woche der Schwangerschaft und natürliches Stillen von Neugeborenen bedingt. Daraus ergibt sich die Notwendigkeit der Durchführung einer klinisch zweckmäßigen Untersuchung der Biozönose der Vagina bei den Schwangeren in der 30-32. Woche der Stillzeit und deren anschließenden Korrektion.



Mikroflora des Schleims in Nase und Rachen

Bei der bakteriologischen Untersuchung des Schleims in Nase und Rachen wurden in 42,8% der Fälle aeroben und nicht-klostridialen anaeroben (NKA) Bakterien, in 42,8% - nur aeroben und in 14,2% - nur NKA (Eubakterien, Bifidobakterien, Lactobakterien) isoliert. Unter NKA Bakterien dominierten im Schleim in Nase und Rachen die Eubakterien (57,1%), die in 100% der Fälle aus der Vagina der Schwangeren in der 38. Woche isoliert wurden. Aus dem Schleim in Nase und Rachen von 4 Neugeborenen wurden Enterokokken, von 3 Neugeborenen - S.aureus, von 1 Neugeborenen - E.coli, Bazillen, coryneforme Bakterien isoliert.

Die Bildung der Darm-Mikroflora beim Neugeborenen stellt einen komplizierten Selektionsprozess dar, an dem zahlreiche Mikroorganismen der Mutter und der Umwelt beteiligt sind. Die Entdeckung von Bifidobakterien, Lactobakterien, Escherichia, Klebsiella in den Exkrementen von meisten Neugeborenen, 100% Isolierung von Enterokokken, Staphyllokokken, Besiedlung des Schleims in Nase und Rachen nicht nur mit aeroben, sondern auch mit nicht-klostridialen anaeroben Bakterien zeugen von der «mütterlichen» Herkunft der Stämme und werfen die Frage nach Kolonisierungswegen von Biotopen des Neugeborenen auf.

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Die effektive Lösung der Probleme der posttraumatischen Rehabilitation von Sportlern. Der neue Blick auf das Phänomen des „Phantomschmerzes“

Yury Titarenko

Klinischer Fall:

Der Patient: der 52-jährige Mann, der General der Geheimdienste, die sportliche Leistungsfähigkeit und den (sportlichen) Zustand des Organismus ist höher als die mittlere Norm.

Die Verletzung: die ausgedehnte Knochenzertrümmerung beider unteren Gliedmaßen, die schwere Schlagverletzungen des rechten Unterarmes und des Kopfes infolge des Auffahrunfalls (am Fußgängerüberweg).

Infolge des ausgezeichneten physischen Zustandes vor dem Erhalten der Verletzungen, sowie der psychologischen Vorbereitung, ging die physische Rehabilitation schnell. Nach dem Monat überwand der Patient (die Gehstützen benützend) die Entfernungen bis zum 1 km der Fußspaziergänge pro Tag.

Jedoch beschwerte sich der Patient über die starken Schmerzen im Bereich des rechten Unterarmes ständig. Das Schmerzsyndrom weitete sich ab 23-00 (täglich) aus und reduzierte sich ungefähr um 6 Uhr morgens.

Im Laufe von den nachfolgenden 3 Monaten war das klinische Bild unveränderlich, obwohl der Zyklus der medikamentösen, physiotherapeutischen und Akkupunktur- Intensivtherapie unternommen wurde. Auch war der Patient ein Grund der mehrfachen Konsillien mit der Teilnahme der führenden Fachkräfte der Militär- und bürgerlichen Medizin.

Auf einem der Konsillien, von dem Autor dieses Artikels war die Version der Hypothese darüber ausgestellt, dass das Schmerzsyndrom, das den Patienten empfindet, nicht etwas Anderes als „die psychosomatische Reaktion“ ist und der Behandlung eben mit den psychotherapeutischen Mitteln unterliegt.

Hier ist es nötig zu bemerken, dass der Patient die spezielle Sitzung von „der posttraumatischen Stresses-Analyse ™“ sofort nach dem Erhalten der Verletzungen (am 4. Tag) bekommen hat und gerade es hat die schnelle, produktive Heilung der Brüche und der Schäden der unteren Gliedmaßen am meistens versorgt. Jedoch an diesem Moment machte der Patient keine Bemerkungen über die Probleme mit dem Unterarm, und die Psychoverletzung vom Schaden des rechten Unterarmes war Stress-analytisch nicht behandelt.

Selbst der Patient hat das Einverständnis mit der Vermutung über das psychosomatische Entstehen des Syndroms geäußert, und hat nochmal um die Durchführung der Sitzung der Stresses-Analyse ™ gebeten. Es war die 40-Minuten-Sitzung durchgeführt. Am nächsten Tag hat der Patient mitgeteilt, dass er zum ersten Mal während drei letzten Monate den vollkommen gesunden tiefen Schlaf durch die ganze Nacht ohne irgendwelche Schmerzempfindungen hatte.

Jedoch bei der Durchführung des Konsiliums, die Idee über die Gründe des Schmerzsyndroms des rechten Unterarmes, als „psychosomatischen“, von der Mehrheit der Fachkräfte, die am Konsilium teilnahmen, abgelehnt war, was die Notwendigkeit verursacht hat, die notwendige Beweisbasis unter die vorliegende Hypothese zuzuführen.

Alle mögliche Untersuchungen des Zustandes des verletzten Unterarmes vom Patient brachten zur Schlussfolgerung darüber, dass irgendwelche wesentlichen Veränderungen in den Knochen und den weichen Stoffen, die als ein Grund des Schmerzsyndroms sein könnten, fehlen. Deshalb war die Vermutung über das Entstehen des Schmerzsyndroms, hypothetisch ähnlich dem Phänomen, s.g. „der Phantomschmerzen“, eben aufgestellt.

In der klassischen Medizin betrachtet man ein Herangehen an das Problem „der Phantomschmerzen“, als an das Problem, das von den irreversibelen Veränderungen des Nervengewebes an der Verletzungsstelle (der Amputation) verursacht wird.

Das Zitat. „Die Phantomschmerzen in den Gliedmaßen ist eines von den ernstesten Schmerzsyndromen. Zum ersten Mal waren sie im Jahr 1552 von Ambroise Paré beschrieben, aber bis jetzt sind die Mechanismen, die in ihrer Grundlage liegen, nicht ganz geforscht, und die Methoden ihrer schnellen Beseitigung fehlen praktisch.

Das Prozent der Amputierte, die nach den Phantomschmerzen leiden, ist merkwürdig hoch. Eine von den ausführlichsten Forschungen auf diesem Gebiet (Jensen et al., 1983, 1985) hat gezeigt, dass die Phantomschmerzen bei 72 % der Amputierte schon in den ersten 8 Tagen nach der Operation entstanden, nach 6 Monaten wurden sie bei 65 %, zwei Jahren später - bei 60 % bemerkt. Laut den Angaben von Krebs et al., beschweren sich 60 % der Amputierte über die Schmerzen in der Phantomgliedmaße auch nach 7 Jahren weiter. Diese Angaben werden auch von anderen Forscher (60 %: Carlin et al., 1978, 78 %:Sherman et al., 1984) bestätigt. Jedoch im Laufe der Zeit werden die Schmerzangriffe seltener sein. Nach den Materialien der ernsten Forschung unter den Veteranen des Krieges in den USA, erreichen die Phantomschmerzen und die Schmerzen im Amputationsstumpf von 85 % der Befragten solche Stärke, dass die Arbeitsfähigkeit und der soziale Status des Patienten (Sherman et al., 1984) verletzt werden.

Ungeachtet des Daseins mehr als 40 Methoden der Therapie des Phantomschmerzsyndroms (Sherman et al., 1980), befreien sich nur 15 % der Kranken von diesem Leiden vollständig, dass die Folge von keinen vollen Verständnisses der Mechanismen, die das Entstehen den Phantomschmerzen bedienen, möglicherweise ist.“

„Die Amputation der Gliedmaße ist kein einziger Zustand, bei dem das Phantom entsteht. Das schmerzlose Phantom wird oft von den Patienten mit dem lokalen Block der Sensibilität des irgendwelchen Körperteils beschrieben. Es war doch von Simmel (1962) bei den Patienten mit den Schäden des Rückenmarks, von Melzack und Bromage (1973) bei den Patienten mit den Schäden des Schultergeflechtes beschrieben. Beim Block des Schultergeflechtes wird das starke Jucken, Stechen in der Phantomhand verspürt. Der

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Patient fühlt besonders deutlich die Stellung der Hand, der Finger im Raum (Melzack und Bromage, 1973, 1974).

Es bringt auf einen Gedanken, dass die Wahrnehmung des Phantoms vom Zusammenwirken der Funktionszentren der Gehirnrinde, die für den Aufbau des Körpers antworten, bedingt ist."

„Nach dem Charakter kann man die beschriebenen Schmerzen auf 3 Gruppen teilen: mit dem Dominanz vom „kausalgischen" (brennenden) Schmerz, mit dem Dominanz vom „neuralgischen" Schmerz (ähnlich dem Stromschlag) und mit dem „Krampi" ähnlichen Schmerz (krämpfig, zusammenpressend). Sie können unmittelbar nach der Amputation anfangen, und manchmal entstehen die Wochen, die Monate und sogar die Jahre später.

Die Gefühlserlebnisse, der Stress können die Verstärkung der Schmerzen herbeirufen. Dabei sind die operativen Einmischungen, solche wie Neuro-, Radikulo -, Sympathikotomie und andere, oft erfolglos. Der Patient kann einer ganzen Reihe der chirurgischen Eingriffe ohne bedeutsame Senkung der Intensität der Schmerzen untergezogen sein. (Henderson und Smyth, 1948)."

„Historisch geht die Suche der Mechanismen, die der Phantomschmerzen bilden, von der Peripherie zum zentralen Nervensystem. Die frühste chirurgische Methode der Behandlung war die Entfernung der Nerven, die sich auf dem durchgeschnittenen Nerv entwickeln und die normale Regeneration behindern. Die folgende Etappe ist das Durchschneiden der sensiblen Wurzel in das Rückenmark. Beide diese Methode haben sich als uneffektiv erwiesen, sowie die Unterbrechung von Nervenbahnen im Rückenmark. Sie bringen nicht nur keine langdauernde Erleichterung, sondern auch bringen die Verstärkung der Schmerzen, dem Unbehagen oft. Die Sympathikotomie ist auch gemäßigt wirksam. Auf der Unterbrechung der afferenten Schmerzimpulse gründen sich doch die stereotaktischen Operationen auf den Thalamuskerne.

Insgesamt sind alle chirurgischen Methoden der Behandlung der Phantomschmerzen verhältnismäßig uneffektiv anerkannt. " (N.S.Pavlenko, Novosibirsk Fond SAPF ©)

So wie wir aus dem obendargelegten Material sehen, haben die Versuche der Lösung der Probleme „der Phantomschmerzen" von den Methoden der Chirurgie, der Pharmakologie, der Physiotherapie, sowie von verschiedenen alternativen Methoden, keine wirksamen Ergebnisse bis jetzt gegeben. Es werden die Fälle der Verbesserung beobachtet, die nicht systematisiert sein können, und die Therapie, die zur Verbesserung brachte, kann zur öffentlichen Anwendung mit der Garantie der Verbesserungen nicht empfohlen sein.

Da das Problem der Phantomschmerzen von der Medizin innerhalb von nicht eines Jahrhundertes betrachtet ist, so wurden die verschiedene Erklärungen und Vermutungen bezüglich ihres Entstehens von religiös (so wie – „die Strafe für die Sünden") bis philosophisch-psychologisch (darüber, dass es die Erscheinungsform „der Seele", die „den Körper in einer bestimmten Weise einprägt hat", ist) entsprechend gemacht.

Einer erster, wer begonnen hat, ein Problem der Phantomschmerzen vom Gesichtspunkt der Psychologie und der Kanons der Psychotherapie zu betrachten, waren Doktor Sigmund Freud (Freud, Sigmund) und Doktor Josef Breuer (Breuer, Josef). Die Benutzung der Methode „der psychologischen Katharsis" gab schon damals eine bestimmte positive Statistik bei der Behandlung der Veteranen. Die Methode hat aber keine öffentliche Anwendung in der vorliegenden Problematik wegen der Teuerung und der Komplexität bekommen. Die Medizin betrachtete mehr materialistischen und weniger teureren, hauptsächlich chirurgischen und pharmakologischen, Wege.

Jedoch geben die modernsten Forschungen auf dem Gebiet der subatomaren Quantenphysik, sowie der höchsten funktionalen Hirnrindentätigkeit, die Gründungen, zu vermuten, dass der Schmerz fähig ist, als „das abgesonderte physische Objekt", das die energetische Natur und Struktur hat, die mit den physischen Hauptparametern bestimmt sind: die Gespanntheit, den Umfang, die Temperatur, die potentielle Energie (die Fähigkeit zur „nützlichen" Arbeitsausführung), die Stellung im Raum, etc., zu existieren.

Wenn die Tatsache dabei zu berücksichtigen, dass das Gehirn fähig ist, solche „energetischen Strukturen" in sehr komplizierten Form zu produzieren, so bietet sich die Schlussfolgerung darüber an, dass wenn diese Objekte fähig sind, von der Gehirnstätigkeit aufgebaut zu sein, so können sie bei der bestimmten geistigen Bemühungen auch von ihm ABGEBAUT werden. Und solche Vermutung ist absolut richtig.

Jede Verletzung ist vom Verstand, als die Reihenfolge der Veränderungen des physischen Zustandes des Organismus und der Abänderung seiner Formen festgehalten.

Dieser Prozess wird vom Verstand fixiert und ist dann für den Verstand so eine Art von der ANWEISUNG danach, wie der Zustand des Organismus nun sein soll. In dieser Situation ist der Schmerz ein untrennbarer Bestandteil dieser „Anweisung". Der Verstand betrachtet eine Speicherung dieses Schmerzes, als die notwendige Bedingung für die weitere Tätigkeit des ganzen Organismus in „den neuen Bedingungen" und der Verstand ist wieder und wieder fähig, den Schmerz, nur wie ein Teil des Programms der Lebenserhaltung, zu reproduzieren.

In diesem Fall kann man jeden psychosomatischen Schmerz (d.h. der Schmerz, der durch keine konkrete laufende Reizung eines Nervenstamms hervorrufbar ist) als der „Phantomschmerz" (oder psychosomatischer Schmerz) betrachten, und das Entstehen dieses Schmerzes steckt gerade in der Bildsystem dahinter, die vom Gehirn (dem Verstand) im Moment der realen Verletzung und auch, als die Folge, die reale Verletzung aufgenommen ist.

Jeder posttraumatische Schmerz kann als die Erscheinungsform des Phänomens des Phantomschmerzes betrachtet werden.

Die Befreiung von solchem Problem steckt in der feinen persönlichen psychotherapeutischen Betreuung des Patienten dahinter, wo sich die Aufmerksamkeit des Patienten auf die psychoverletzenden Emotionen (die Verletzung, der Unfall) vielmals gerichtet wird, und solches mehrmaliges Erleben der Psychoverletzung lässt zu, die Programme des Verstands, die den Phantomschmerz enthalten (und festhalten),

„zu neutralisieren". Die vorliegende Prozedur hat die tiefe wissenschaftliche Begründung (Lessing, Bernays, Zeller, Freud, Breuer, Atanasov u.a.) und gehört zu den grundlegenden psychotherapeutischen Prozeduren (der Methodik des Altersrückschritts (age regression)). Die Methodik trägt den Titel „die posttraumatische Stress-Analyse ™".

Die Problematik „des Schmerzes" in der posttraumatischen Periode (und insgesamt die Aufgabe der schnellen Genesung der Patienten) kann nun in der Hinsicht der Anwendung der psychotherapeutischen Methode betrachtet werden, als der Vorrangige im Zyklus der unternommenen Maßnahmen. Die Effektivität der Anwendung der Methodik erreicht 96-98 %.

So wurde, zum Beispiel, die Methodik „der posttraumatischen Stresses-Analyse ™" für die Fälle der Rehabilitation der Sportler vielmals verwendet. Im solchen Fällen wurde nicht nur die außerordentlich schnelle Genesung der Patienten, sondern auch die Abwesenheit „des Syndroms der Neigung zur nochmaligen Verletzung" und „der Angst vor die nochmalige Verletzung" danach beobachtet. Diese psychologischen Phänomene sind in den Materialien der Sportmedizin mehrmals beschrieben.

Der typische klinische Fall:

Der 23-jährige Mann, der Meister in der Sportakrobatik, der Meister in Taekwondo.

Die vielfachen Verletzungen des rechten Knies. Es ist die Entscheidung über die Unterbrechung der sportlichen Karriere getroffen.

Es sind 2 Sitzungen „der posttraumatischen Stresses-Analyse ™" (insgesammt – 4 Stunden 20 Minuten) durchgeführt.

Die Rehabilitation auf dem physischen Niveau war im Laufe von 2 Wochen. Das Ergebnis: die absolute Beweglichkeit, das volle Verschwinden des Schmerzsyndroms.

Die psychologische Rehabilitation ist im Prozess der stress-analytischen Sitzung getreten. Es gab die Erneuerung des Interesses für die sportliche Karriere und kein Angst vor den Belastungen oder die potentielle Verletzung.

Der typische klinische Fall:

Der 28-jährige Mann, der Meister des Sports der internationalen Klasse im Fußball, der Stürmer. Die vielfachen Kniegelenkverletzungen beider Beine. Die langdauernde Rehabilitation mit dem ausgedehnten Schmerzsyndrom.

Es sind 6 Sitzungen „der posttraumatischen Stresses-Analyse ™" (insgesamt 14 Stunden) durchgeführt.

Die Rehabilitation auf dem physischen Niveau war im Laufe von 3,5 Wochen. Das Ergebnis: die absolute Beweglichkeit, das Verschwinden des Schmerzsyndroms auf 95 %.

Die psychologische Rehabilitation ist im Laufe der Setzungen getreten. Es gab die Erneuerung des Interesses für die sportliche Karriere und das tatsächlich volle Verschwinden der Angst vor den Belastungen oder die potentiellen Verletzung.

Characteristics of life quality of patients with compressive forms of lumbar osteochondrosis diagnosis.

Elena Ukhvatova

Nowadays one of the main criteria of medical aid efficiency is an acceptable life quality renewal and an adequate social adaptation of patients. At the same time an insufficient attention is paid to life quality assessment of patients with lumbar osteochondrosis diagnosis today.

The objective of the given work is an assessment and the comparative analysis of life quality of patients with compressive forms of lumbar osteochondrosis diagnosis during metabasis.

In the process of complex medical measures to ascertain the degree of disability a research of life quality of 114 patients with compressive forms of lumbar osteochondrosis (inquirer the Rand 36) was made.

The comparative analysis of the results received and the average rate of test revealed a decrease of general health indicator of 56 patients (49,1%), that may be due not only to reduce in physical functioning (lower than normal in 52.6% of cases), but also the emotional well-being (lower than normal in 62.3% of cases). 55 patients (48,2%) suffered from decrease in social functioning, that may reveal the

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disarrangement of social adaptation, which is the basis of inadequate employment opportunities and the need for premature disability.
The earlier conducted complex clinical and appliances inspection of the above mentioned patients allowed exposing of different forms of lumbar osteochondrosis: radikulopaticheskaya and radikulocerebral'naya. The largest amount (98,2%) of the exposed psycho-emotional disorders (depression and anxiety) and significant decline of life quality is noticed for patients with a radikulocerebral'naya form.
The findings suggest the conjugation of life quality of patients with lumbar osteochondrosis with these forms of disease, and it must be considered when treating the spine pathologies.

Besonderheiten der Businessplanung in einem kleinen Pharmaunternehmen

Oksana Umnowa

Unter der Bedingungen der Finanzkrise müssen alle Teilnehmer den Kampf um das Überleben führen: von den großen Pharmaunternehmen bis zu den gewöhnlichen Apotheken. Die Schwierigkeit der Apothekenunternehmen (gekürzt: AU) besteht darin, dass sich die Leiter nicht genug in den modernen Businesstechnologien zurechtfinden[1]. Ihr Ziel ist nicht nur Gewinnerwirtschaftung, sondern auch die Teilnahme an dem Prozess der Verbesserung der Gesundheits- und Lebensqualität der Bevölkerung[2].
Der effektiven AU-Führung hilft die Businessplanung. Bei der Ausstellung der Businesspläne (gekürzt: BP) der Pharmaunternehmen (gekürzt: PU) muss man die Spezifik des Arzneimittelmarkts berücksichtigen.
Erstens, dieses Business hat Sozialfunktionen, die von der Gesetzgebung und den normativen Grundlagen hart geregelt werden. Zweitens, der Kunde besorgt Medikamente in der Apotheke zur Erhöhung der Lebens- und Gesundheitsqualität. Dieser Kauf fordert oft Arzt- oder Pharmazeutberatung. Deswegen sind die besonderen Forderungen zur Ausbildung der Fachkräfte, Angebotskenntnis, Kenntnis der pharmakotherapeutischen Wirkung der Arzneimittel und der Verkaufsverfahren nötig. Drittens, das Vertrauen der Kundschaft: 7 von 10 Kunden besorgen die von den Pharmazeuten empfohlenen Medikamente [3].
Die Gelehrten [3,4] haben die Hauptfaktoren der Verkaufseffizienz in den AU ausgesondert und die Aufgaben für die moderne Führung bestimmt. Es geht nämlich um: 1) die Lage der Apotheke; 2) die Warenpolitik; 3) die Preispolitik; 4) Nebenleistungen; 5) die Apothekenausstattung; 6) die Verkaufsleistungsfähigkeit; 7) die Einträglichkeit der Apotheke; 8) die Fahrbereitschaft; 9) die Waren- und Apothekenbewegung; 10) der Personalprofessionalismus; 11) die Lagerablauforganisation; 12) die Einheit der Verkaufsprozesse.
Die Analyse der Organisation der Bevölkerungsarzneimittelversorgung ermöglichte die Aussonderung der Hauptprobleme, deren Lösung von der erstrangigen Bedeutung ist. Das ist das Fehlen des objektiven Bewertungssystem und des Monitorings der Effizienz der AU-Betriebsfunktion, das Fehlen des Zusammenhangs zwischen dem Umsatzvolumen und dem anfallenden Gewinn, die Unterschätzung der Bedeutung der Innovationstechnologien.
Abhängig von den prognostizierenden Zielen und Aufgaben können drei Typen der BP erarbeitet werden [5]:
- BP des Unternehmens ist die Zukunftsentwicklung des Unternehmens für die prognostizierende Periode unter Angabe der hauptfinanzwirtschaftlichen Kennziffern der Tätigkeit für die Begründung der notwendigen Ressourcen;
- BP der Organisationseinheit ist der Plan der Einheitswirtschaftstätigkeit für die Begründung der Volumina und des Rangfolgengrades der gegebenen Ressourcen;
- BP ist als eine Kreditantragsstellung für die Aufnahme der Anleihe auf dem Kommerzgrund vom Unternehmen-Gläubiger.
Die Entwicklung der methodischen Ansätze in Businessplanung ist in Pharmazie notwendig. Der professionell richtig erarbeitete BP hilft dem Unternehmen bei der Entwicklung und der Stärkung der Marktposition,

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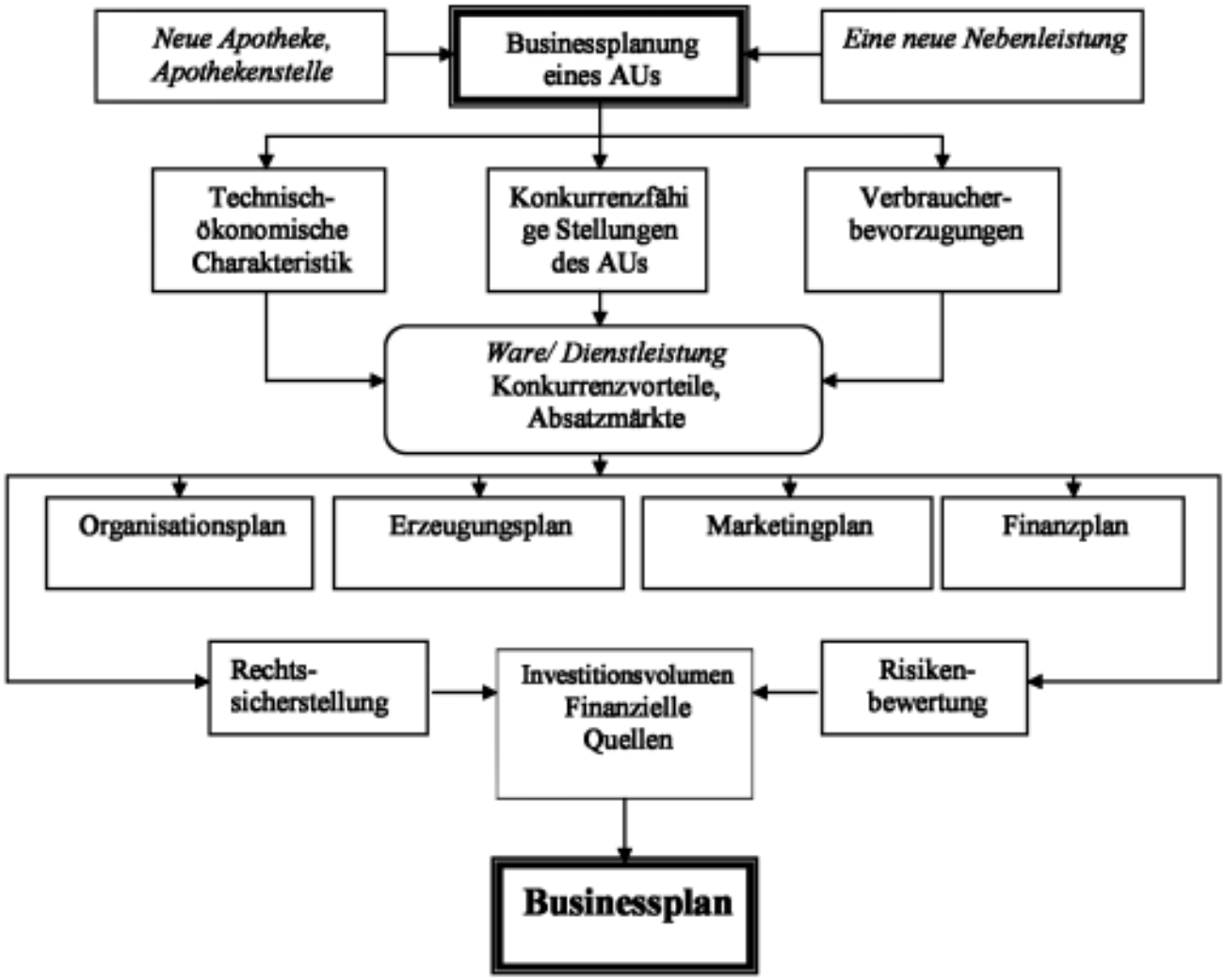

Bild 1. Das Modell der Businessplanung der Tätigkeit eines AUs

der Tätigkeitsmodellierung auf Grund der modernen Prinzipien in Management, Marketing, Wirtschaft des Unternehmens[6].

Die Verfasserinnen haben ein Modell der BP für ein AU erarbeitet (Bild 1).

Dem Modell entsprechend sind die methodischen Empfehlungen der stufenweisen Planung für die Eröffnung einer neuen Apotheke, einer Apothekenstelle oder der Einführung einer neuen Nebenleistung vorbereitet. So in der 1. Stufe wird die Notwendigkeit der Angabe der kurzen Entwicklungsgeschichte des AUs in der Zusammenfassung begründet. In dem Kapitel der Rechtssicherstellung des Projekts werden die rechtlichen Aspekte der Sicherstellung der Unternehmensgründungs- und Unternehmensfunktionsprozesse gegeben. Die Unternehmensform des AUs wird bestimmt.

Für den russischen Pharmamanagement ist die Marketingplanung (gekürzt MP) eine neue Methode. Die Hauptbesonderheit des Marketingplans ist der Versuch die Kundschaftsbedürfnisse mit dem Gewinn fürs Unternehmen zu vereinbaren. Auf Grund der MP wird BP zusammengesetzt. Das ist der Entwicklungsplan der neuen Arbeitsbereiche des AU, der Gründung der neuen Geschäftsarten. Die Marketingforschungen der Verfasserinnen haben gezeigt, dass sich der russische Pharmamarkt dynamisch entwickelt. Es wurde festgestellt, dass der Medikamentenkonsum eine von den Branchen ist, in der der Verkauf 2009 nicht zurückgegangen ist, sondern den Zuwachs gezeigt hat. Der Medikamentenkonsum in dem Segment des Kommerzsektor ist mehr als um 20 % in dem Wertausdruck gewachsen. Der hohe Wert aber ist meistens von dem Preisanstieg, nicht aber von dem Zuwachs in der Naturangabe bedingt.

Die Bewertung der Konkurrenzpositionen des AUs auf den Pharmamarkt wird in der Regel auf Grund der Konkurrenzumgebungsanalyse verwirklicht. Es ist wichtig die wirklichen und die potenziellen Konkurrenten zu bestimmen, die Analyse der Angaben ihrer Tätigkeit, ihrer Ziele, Strategien zu führen, ihre starken und schwachen Seiten einzuschätzen. Die Vergleichsanalyse des AUs mit den Konkurrenzpositionen hilft die eigene Position auf dem Markt bestimmen. Die Präferenzen der speziellen Verbrauchersegmente ermöglichen die Erarbeitung des Marketingplans in der Waren- oder Leistungsbewegung. Die Analyse des potenziellen Verkaufsmarktes ist eine obligatorische Stufe in der Erarbeitung eines BP. In dieser Stufe ist es nötig eine Umsatzvolumenvorhersage zu entwickeln, was bestimmte Schwierigkeiten hat, denn ein AU kann über keine Statistikinformation über Absatzvolumina der Konkurrenten verfügen. Laut den Angaben der BP- Apothekeneröffnung, der von den Fachkräften der Gesellschaft GLOBAL REACH CONSULTING entwickelt wurde, 2009 haben die führenden Apothekeneinzelmarktteilnehmer Russlands die Politik der Businessführung verändert und beschäftigen sich mit der Optimierung und

Nutzeffektsteigerung der bestehenden Apothekenstellen. So zum Beispiel „Apothekennetz 36,6“ hat sich fast um 100 Apothekenstellen im Vergleich zu 2008 verringert, „Doktor Stoletow“ hat sich um 40 Apothekenstellen verringert. Der Anteil der zehn Besten hat sich 2009 fast um 4% verringert.
Der Organisationsplan hat ein Kapitel, in dem das Stammpersonal der neuen Leistung erarbeitet wird. Die Kriterien der Personalforderungen, Dienstpostenplan werden bestimmt, Planlohnfonds werden errechnet usw. Im Produktionsplan muss Produktionsbasis, Rohstoffe und Energie, Arbeitsvermögen, Technologienversorgtheit, betriebsfixe und variable Kosten, Berechnung des Selbstkostenpreises, Produktionsqualitätsprüfung gezeigt werden. Die Finanzanalyse ist eines der wichtigsten Steuerelemente. Die Methoden der Finanzanalyse nutzen alle Anwender der Finanzberichterstattung, darunter Kapitalanleger für die Begründung ihrer Investitionen in den BP [7]. Es gibt auch methodische Ansätze in der Durchführung der Schnellbestimmung der finanziell-wirtschaftlichen Tätigkeit des AUs. Die Technologien der Schnellbestimmung der Finanzkrise, der Verwendung der inneren Reserve und der Finanzstabilisationsmechanismen sind in der Arbeit von 17 AU approbiert. Im Finanzplan müssen die Werte der Finanzsicherung der AU-Tätigkeit und der Plan der Nutzung von den bestehenden Finanzmitteln gezeigt werden. Das Kapitel, das der Risikoeinschätzung gewidmet ist, ist auch nötig, denn man muss in BP die alternativen Strategien und Kompensationsmaßnamen vorsehen. Jede aus dieser Formen hat ihre Besonderheiten, die im bestimmten Grad den BP-Verwirklichungserfolg beeinflussen können.
Schlussfolgernd nach den Ergebnissen aller Kapitel des BPs wird das notwendige Investitionsvolumen, ihre vermutete Struktur (die eigenen und die geliehenen Mittel) bestimmt, der Zweckmäßigkeitsattest des AUs wird gegeben. Bei der BP-Erarbeitung muss man zwei möglichen Firmenentwicklungsstrategien berücksichtigen. Dafür muss man zwei Entwicklungsmodelle der Firma auszeichnen: das klassische oder das innovative (das Venturamodell, das riskanteste Modell).

Zusammenfassung

1. Die moderne Apothekenveranstaltung setzt die Erarbeitung des BPs voraus, mit dessen Hilfe die Verwirklichungsstrategie der Innovationsprojekte, der planbaren Kosten und Ergebnisse begründet wird.
2. Die BP-Struktur wird für die gesetzten Ziele und Aufgaben in der Verbesserung der Medikamentenproduktion und Arzneibedienung, die Verstärkung des Zustandes und der standfesten Marktpositionen adaptiert.

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Diagnostics and treatment of allergic diseases in naturopathy

Gamzat A. Yusupov

Objective: Study the possibility of energy-information diagnostics in identifying etiological factors and the effectiveness of treatment with non-pharmacological preparations based on quantum-wave (energy-information) characteristics of etiological factors, homeopathic preparations, potentiated metabolic products, and organo-preparations, selected on a case by case basis.
Methods: Authorized modification of the R. Voll procedure is used for diagnostics and selection of an optimal combination of quantum-wave therapeutic components. Original equipment, software, and methodology, Apparat-programmic complex “UPRANA- Pro” was used for analyzing energy-informational diagnosis with medical testing.
Electric-acupunctural study of electric conductivity dynamics characteristics of biologically active points in patients suffering from various forms of allergy was conducted – 217 in all,

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ages 14 through 57. A test of quantum-wave characteristics of bacterium, virus, protozoa, and parasite nosodes identified etiological factors present in the organism of patients surveyed. Treatment was based on quantum-wave characteristics of etiological factors, homeopathic preparations, and potentiated metabolic products, selected on a case by case basis.
Results: Various etiological factors were identified. The character of symptomatic manifestations was to a very large extent predicated on a combination of pathogens identified in an individual patient. Testing showed that virtually all patients had an immune problem, apparently resulting from a Cytomegaloviral infection or the Epstein-Barr vir. The study established that localization and specifics of allergic manifestations were contingent primarily on etiological factors identified. Symptomatic manifestations disappeared following a course of treatment designed to eliminate etiological factors. In the event of a recurrent allergy, repeat testing identified new pathogenic factors. A change in a combination of pathogens brought about a change in pathogenic manifestations.
Conclusions: energy-information procedure shows good potential in combination with other methods of addressing allergic problems.

Infertility. Naturopathic diagnostics and etiotropic treatment

Gamzat A. Yusupov

Objective: study of the possibility of energy-information diagnostics in identifying etiological infertility factors and the effectiveness of treatment with specific quantum-wave (energy-information) non-pharmacological preparations selected on a case by case basis.
Methods: Authorized modification of the R. Voll procedure is used for diagnostics and selection of an optimal combination of quantum-wave therapeutic components. Electric-acupuncture study of electric conductivity dynamics characteristics of biologically active points in infertile patients. Medicinal nosode testing identified etiological factors present in the organism of patients surveyed. Treatment was based on nosodes identified through patient testing and etiological factors (toxic products of microbial/viral and environmental origin) in combination with homeopathic preparations. At the final therapy stage, preparations with quantum-wave characteristics of organo-preparations were used in combination with constitutional homeopathic compounds, which were also selected through testing. Apparat-programmic complex "UPRANA-Pro" was used for analyzing energy-informational diagnosis with medical testing. In all, 38 women, ages 23 through 41. Treatment administered at other clinics, including homeopathy, reflexotherapy, and other alternative methods, proved unsuccessful.
Results: The following etiological factors were identified (in 94 percent of cases): viruses – Parotitis, Herpes proginetalis, Cytomegalie, V. Epstain-Barr, Rubeolae; bacteria – Gonococcus, Staphylococcus aur., Brucella, Bac. lactis, Micob. Tuberculesis; protozoa – Chlamydia trachomatis, Trichomonaden fluor, Myccoplasma hom, Lysteria, Toxoplasma, Ureaplasma ur., Ureaplasma par., Radionuclides and heavy metals – mercury, lead, and cadmium – were identified in four instances. Anamnesis and the results of clinic and laboratory tests did not always coincide with the results of quantum-wave diagnostics. Etiological factors were identified in various combinations. Coincidence of established etiological factors was, as a rule, matched by a coincidence of clinical results. Thus, in tubal adhesion related infertility, the resonance effect occurs in testing the quantum-wave characteristics of the Parotitis virus and pathogens causing topical inflammation. In hormonal imbalance related infertility, factors affecting ova and neurohypophysis are identified: viruses, Toxoplasmose, radionuclides, and heavy metals. Research shows that every microbial/viral etiological factor is matched by a certain homeopathic preparation: Chlamydia – Conium, trichomonas – Helonias, and so forth. Of 38 women who underwent a full course of treatment, 22 got pregnant within three months and seven, within five to eight months after completing the course. One patient had extrauterine pregnancy, in the sole tube. Others remain under surveillance. It is noteworthy that virtually all pregnancies were toxicosis-free.
Conclusions:
1) quantum-wave diagnostics with etiological factor nosode testing helps establish case-specific infertility causes;
2) treatment with energy-information therapeutic agents based on a case-specific selection of quantum-wave characteristics of nosodes and homeopathic preparations is a fairly effective infertility treatment method;
3) further study of energy-information diagnostics and therapeutic methods has good scientific/practical prospects, in particular in addressing the infertility problem in combination with existing methods

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