Rakitskaya E.V. [1], Uchakina R.V. [2], Efimenko M.V. [2], Kozlov.V.K. [2]

Vegetative dysfunction syndrome in adolescents as an integral factor of the high risk for cardiovascular and endocrine diseases in young people: a pathogenetic substantiation of prevention programs

GOU VPO Far-Eastern State medical university
Ministry of health care and social development of Russian Federation[1], *Khabarovsk, the Russian Federation*
Khabarovsk branch FGBU "Far Eastern Research Center of Physiology and Pathology of Respiration" Mother and child care institute [2], *Khabarovsk, the Russian Federation*

Summary: Survey of 1200 young people with vegetative nervous system dysfunction revealed the presence of pathogenetically significant changes in the major regulatory systems of adolescents: high frequency of mental health problems, complex sub-clinical abnormalities in the immune, endocrine, reproductive systems involving a high level of endogenous intoxication at the cellular and organism level. The project of the program of health monitoring of the mentioned group is developed.

Keywords: health, adolescents, vegetative dysfunction syndrome, risk factors, micro-elements, hormonal regulation, oxidative stress, prophylaxis.

The state of adolescent health is a barometer of social welfare and medical care, a harbinger of public health changes in later years. Nationwide forum "Children's Health - the basis of the nation's health," noted the suspension of the negative trends in the children health status at the national level, but underlined the permanence of high level of adolescents' morbidity (60%), high level of socially important diseases, the presence of psychosomatic and reproductive health disorders of adolescents [1]. The first place among noninfectious disease take cardiovascular disease which are inflicting irreparable economic damage around the world and are the major cause of the population mortality [12]. In Russian Federation, every 5th inhabitant has a typical form of

ischemic heart disease, myocardial infarction "rejuvenated" by an average of 15 years, death rates increased by 20%, reaching 40,8 among men and 5,5 among women under 45 in the group older than 50 these indicators increased by 2,5 times [7,10,11.].

The study of predictors of hypertension and other cardiovascular and metabolic disorders formation in the youth is important [12, 13]. One of the most common abnormalities in adolescent health is vegetative nervous system dysfunction, which frequency reaches 30% in different regions of Russia [2,3]. Over the past 10 years the number of young people in the Far Eastern Federal District decreased by 141,5 thousand people, in the Khabarovsk region – 41,9 people. Consistently high incidence of disease classes, in which formation the determining role plays a hidden flowed autonomic dysfunction, are remaining- endocrine (7,3%), nervous system (7,2%), circulatory diseases (4,4%). Last two indicators' level has increased by 2 times for the last 10 years.

Only since 2010 the number of autonomic nervous system disorders among children of the region increased by 1,5 times (from 669,7 to 977,1 per 100,000 population from 0 to 14 years), among adolescents 15 - 17 years increased by 3,3 times (from 1626,8 to 5413,3 per 100000 population). Identification frequency of disease accompanied by arterial hypertension among adolescents in 2012 amounted 413,3 per 100000 [6]. There are no statistical data for these nosological forms in the Far East Federal District, which presents the underestimation of the significance of autonomic nervous system dysfunction in the formation of children and adolescent pathology. In this case, according to Mother and child care institute research, vegetative dysfunction syndrome (VDS) takes second place in the structure of non-communicable diseases, which served as the cause of hospitalization of adolescents due to a significant health deterioration (72%). This requires a serious revision of the relation of pediatricians to the assessment and treatment of this contingent. In order to optimize treatment and diagnostic measures, a scientific analysis of the factors, influencing the processes of Physiology of adolescents with SVD is conducted.

Methods and materials. A survey of 1200 adolescents with SVD in comparable gender groups has been conducted, the control group consisted of 260 healthy children.. While determining the SVD clinical variants and syndromes, classification by NA Belokon (1987) in modification by EV Neudahin and co-authors (2003) has been used. Clinical data included the study of genealogical, social, obstetric and biological anamnesis and somatic status of a child. Diagnostics of undifferentiated connective tissue dysplasia was carried out based on the presence of visceral-locomotor and phenotypic markers [8]. Evaluation of psychosomatic health and psychological characteristics was conducted by analyzing of data, obtained by questioning of the surveyed

adolescents. Paraclinical tests included general and biochemical blood analysis. Evaluation of immune status included the determination of parameters of cellular immunity (rosette method using monoclonal antibodies: CD3 +, CD19 +; CD4 +, CD8 +; CD16 +, CD25 +; HLA-DR +. Humoral immunity indicators are estimated by the enzyme-linked immunosorbent analysis technique. Neutrophils functional activity indicators (FAN: spontaneous and stimulated) were studied in phagocytic activity tests defining the phagocytic index and phagocytic number (FCH - spontaneous and stimulated). Hormonal status included determination of pituitary- thyroid, adrenal-titeotropina (TSH), triiodothyronine (T3), thyroxine (T4, free thyroxine (FT4), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), estradiol (E2), degidroepiandrotrona-sulfate (DHEA-S), cortisol (C) levels, using enzyme immunoassay (ELISA) method. To evaluate the microelement status, the examination of microelement content has been done: copper (Cu), cobalt (Co), manganese (Mn), selenium (Se), nickel (Ni), lithium (Li) and lead (Pb). Microelement definition was carried out in serum and blood cells by atomic absorption method on spectrophotometer «Hitachi-9000" (Japan). The content of iodide in whole blood was studied by direct potentiometry using ion-selective electrodes ("Kritur", the Czech Republic).

For an integrated assessment of free radical oxidation, chemiluminescent method (CML) has been used. Registration was performed on fluorescent spectrometer LS 50B «PERKIN ELMER». The study of spontaneous and induced Fe 2+ chemiluminescention was determined by U. A.Vladimirov method and co-authors [4]: S-sp – amount of light per 1 minute of spontaneous lightening, which correlates with the intensity of free radicals generation; Sind-1- amount of light per 2 minutes Fe2+ induced hemiluminescention, which reflects the intensity of peroxide radicals accumulation, h 1- fast flash amplitude Fe 2+ - induced hemiluminescention, which shows the lipid hydroperoxides concentration. Hemiluminescention kinetics, which was initiated by H2O2 with luminal, was analyzed according to the following characteristics: h2- max flash amplitude, which magnitude is inversely proportional to substrat peroxide resistance; Sind-2 - amount of light per 2 minutes H2O2 - induced hemiluminescention, which is inversely proportional to antiacid antiradical protection system. The hemiluminescention intensity was measured in millivolts per 1 blood serum and was expressed in relative units. In the statistical analysis of the results, standard techniques of variant statistica such as Statistica for Windows Release 7.0. have been used.

Survey results and discussion. Particular qualities complex of the functioning of the main body regulatory systems, contributing to the formation of somatic, endocrine diseases, reproductive disorders among adolescents with the VDS has been identified. The following factors are identified as pathogenetically significant risk factors of SVD: environmental and school psycho-emotional

strain, contributing to the formation of a high level of neuroticism (56%), emotional instability (42%), tendency to depression among 16% of patients. These factors significantly reduce the quality of life of adolescents with SVD (SF-36 ped) (62,7%), determine low levels of emotional (57,5%) and social functioning (58,5%) during the period of exacerbation. The presence of psychosomatic disorders increases the overall risk of cardiovascular disease by 3 times, arterial hypertension by 1.7 times. The high frequency of concomitant functional disorders of the gastrointestinal tract (75%), musculoskeletal (51%), endocrine (37%) and cardiovascular system (31%) is identified. Among 82% of adolescents with SVD the undifferentiated connective tissue dysplasia is diagnosed (Fig. 1), which presence prove the difference in frequencies of gene polymorphisms of detoxification xenobiotics system, suggesting a low efficiency of detoxification enzymes that increase the sensitivity of the organism to the effects of endo-and ekzokotoksikants [5].

Among the endogenous factors that determine the vegatative dysregulation the most significant are a high level of hereditary burden of cardiovascular (36,2%) and endocrine diseases (24%) in maternal line, perinatal risks, concomitant by chronic hypoxia (67,9%).

Directivity of the neuroendocrine regulation defines the high level of "stress hormones" secretion – prolactin, somatotropin, cortisol, DHEA-s, pituitary-thyroid system activation, positively correlated with disorders of central hemodynamics, brain activity, the degree of cognitive, behavioral and neurological dysfunctions-cal ($r > 0,5$, $p < 0,05$) (Fig. 2). These hormones determine the hypothalamic syndrome symptoms of puberty (15.3% of cases), high frequency of reproductive system dysfunction in 19.3% of adolescents, with a predominance of menstrual disorders among girls (16%), among boys-delayed sexual development (13%), cystic-proliferative changes of gonads in both gender groups (6% and 5%), form a group of high risk of metabolic syndrome developing among young [9].

The specific of trace element metabolism among teenagers with VSD has been studied: in both gender groups of patients with SVD, in comparison with the control, identified significantly ($p < 0.05$) higher levels of iodide (49,16 ± 1,4 and 10,85 ± 0,4 mmol / l, 49.64 ± 1,0 and 16,9 ± 2,16 mmol / l resp.), copper (Cus, 25,4 ± 3,36 and 16,7 ± 0,52 mmol / l; 18,98 ± 0,8 and 15,01 ± 0,76 resp.), cobalt (Cos, 0,35 ± 0,03 and 0,20 ± 0,02 mmol / l, $p < 0.05$) most explicit among boys. Significantly lower concentrations of lead (0,006 ± 0,001 and 0,08 ± 0,02 mmol / l resp. ($P < 0.001$), with the accumulation in its form elements are presented (Pb el 2,01 ± 0,09 and 1,62 ± 0.06 mmol / l resp. ($p > 0.05$), which may indicate an extreme instability of cell membranes, contributing to the formation of cytotoxic effects, occur a powerful "nonspecific" goitrogen, explaining the high

incidence of diffuse nontoxic goiter, diagnosed in 28% of cases. A significant correlation between the trace element imbalances and immune endocrine dysfunction is revealed: high level of TTG ($r = -0,8$, $p < 0,05$), prolactin ($r = 0,8$, $p < 0,05$), growth hormone ($r = 0,9$, $p < 0,05$) cortisol ($r = -0,7$, $p < 0,05$), sex steroids- estradiol ($r = -0,8$, $p < 0,05$) and gonadotropin-releasing hormone, FSH ($r = -0,9$, $p < 0,05$). In such way, the imbalance of Cu, Co, Li, Pb is a pathogenetically important factor which causes a high intensity of compensatory mechanisms, disruption of lipid metabolism (19%), disharmony of physical development (28%), disorders of sexual development.

Studies have shown a marked decompensated activation of free radical oxidation, inhibition of antioxidant systems of antiradical protection, reducing the buffer capacity of ACM detoxification among patients with SVD (Fig. 2). Extremely high level of active oxygen metabolites processing may cause the destruction of proteins, nucleic acids and lipids of biological membranes, damage the membrane complexes, cause cytotoxic effects, which can be regarded as one of the most important pathogenetic factors of parenchymal and endothelial injury, determining the endogenous intoxication level.

The examination of immune endocrine relations shows the involvement of immune and endocrine system of organism in the process of autonomous regulation of competitive interpopulative lymphocytes relations, humoral and nonspecific elements of the immune system. Neurovegetative disorders among adolescents with VSD are developed against a background of relative and absolute lymphocytosis, with an increase of the NK markers expression by 25% (CD16+), and late lymphocyte activation (HLA DR), hypoactivity of phagocytic and T-helper immunity element, low level of antibodies, dysimmunglobulinemia with IgE hyperproduction, decrease of IgG level, which may cause the formation of multi-organ pathology and chronic disease progression (table). Psychosomatic and neuroendocrine disorders deterioration is associated with a sharp tightening of intersystem relations and the reduced number of freedom degrees between the indicators of cellular and humoral immunity and adrenal hormones (cortisol, DHEA-S), sex hormones, gonadotropins (Fig. 2), that the most expressed among adolescents with complicated SVD forms - connective tissue dysplasia, hypothalamic syndrome, symptomatic arterial hypertension.

Conclusions: The received data indicate the presence of pathogenetically significant changes in the major regulatory systems of adolescents with SVD - high frequency of mental health problems, complex sub-clinical abnormalities in the immune, endocrine and reproductive system, accompanied by a high level of endogenous intoxication at the organism and cellular level, trace element metabolism dysfunction and significant intensity of compensatory mechanisms.

The revealed complex of polysystem dysfunction requires the organization of health monitoring system of the mentioned group. The program of "Early diagnosis and prevention of cardiovascular and endocrine diseases among adolescents" might become the key component of the young people help program, which significantly optimizes the system of children and adolescents' health monitoring, embedded today in city health centers of Khabarovsk and Khabarovsk region. The program aims: creation of unified methodological approaches to the timely identification of risk groups; improvement of pathology detection, optimization of treatment results in primary care; adolescents' life quality indicators improvement, professional guidance according to the identified pathology.

Guidelines of clinical management should be:

(4) Medical and psychological counseling, adolescent and family support.

(5) Psychosomatic health primary screening based on the adolescents' life quality assessing (SF36 ped) as a technique of dysfunction severity and direction estimating, as well as monitoring of rehabilitation measures effectiveness.

(6) Biological and acquired risk factors, connective tissue dysplasia markers, endocrine dysfunction analysis, based on a questionnaire.

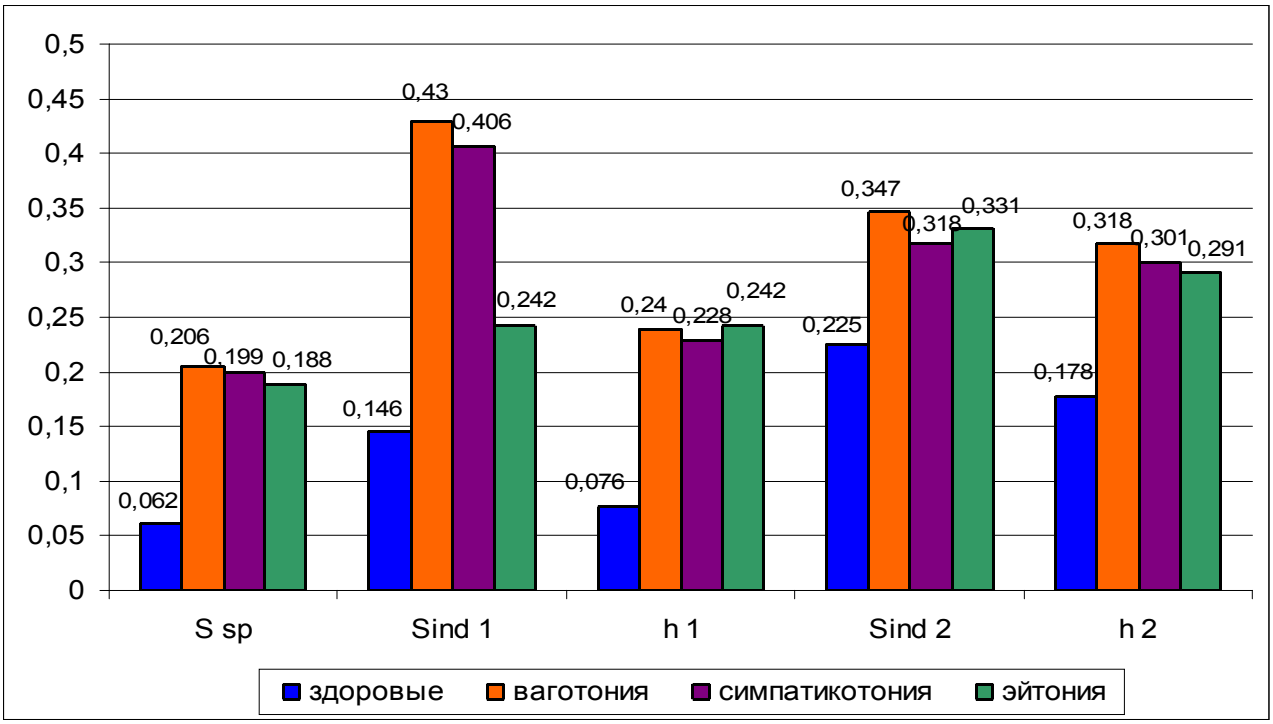
(7) Implementation of teenager's health passport, which includes the expansion of the laboratory and instrumental research complex, including lipid profile analysis, glucose, calcium, phosphorus, uric acid level analysis; hormonal status (TSH, FT4, prolactin, cortisol, LH, FSH, estradiol, testosterone); endocrine glands ultrasound - thyroid, adrenals, gonads; oxidative and trace element status determination- as disease severity and prognosis markers.

5) Individual indications - DNA-diagnostics of endogenous detoxification, cardiovascular disease predisposition, immunological examination.

VSD medical treatment, in addition to the basic neuro-and sedative drugs, should include a pathogenetically substantiated therapy using drugs with antioxidant, membrane stabilizing and detoxifying effects, hormonal imbalance elimination. Organization of medical and counseling help for young people with VDS must be done by such specialist as pediatrician, neurologist, endocrinologist, gynecologist, andrologist, geneticist, psychologist, social worker. Timeous interdisciplinary and interdepartmental intervention of specialists will help to optimize treatment quality, prevent psychosomatic, cardiovascular, endocrine pathology progression risks among young people.

References:

1. Baranov A.A. Actual problems of preserving and strengthening the health of children in the Russian Federation / A.A. Baranov, A.G. Ilyin // Russian Journal of Pediatrics. - 2011. - N 4. - P. 7-12.
2. Autonomic dysfunction in children and adolescents / I. L.Alimova, ed. L.V. Kozlova. - M.: GEOTAR-Media, 2008. – 96p.
3. Wayne A.M. Autonomic disorders: clinics, diagnostics, treatment / A. M.Wayne. – M.: MIA, 1998.-749 p.
4. Vladimirov Yu.A. Free radicals in living systems / Yu.A. Vladimirov, O.A. Azizova, A.I. Deev // Results of science and technology. Ser.biofizika.- M.: VINITI AN SSSR.,1991. - V.29. - 147 p.
5. Genova O.A. Prevalence and some clinical and pathogenetic aspects of the non-differentiated connective tissue dysplasia in adolescents: thesis abstract of PhD (medicine): 14.01.08 / O. A. Genova; Far Eastern State Med. Univ RF MZ I SR. - Khabarovsk, 2011. - 26 p.
6. Child's population morbidity of Khabarovsk Territory 2011 // Collection of statistical materials; Medical Information Center of the Ministry of Health of the Khabarovsk Territory. Khabarovsk, 2011. – 47p.
7. Leontyeva I.V. Risk factor for atherosclerosis and coronary heart disease in children and adolescents /I.V. Leontyeva // Lectures on preventive and prophylaxis pediatrics/ ed. Yu.E. Veltischev.- M.. SRI of Pediatrics and Pediatric Surgery. - 2005. – 60p.
8. Nechayeva G.I. Connective tissue dysplasia: prevalence, phenotypic signs, associations with other diseases / G.I. Nechayeva, I.A. Viktorova, I. Druk / / Vrach. - 2006. - № 1. - P.19 -23.
9. Rakitskaya E.V. The health status of adolescents with hypothalamic syndrome of puberty / E. V. Rakitstaya, R.V. Uchakina, V.K. Kozlov // Yakut medical journal. -2011. - № 3 (35). - P.14-17.
10. Chisolm Slemmer J.E.,Shacka J.J., Sweeney M.I. et al.Antioxidants and free radical scavengers for the treatment of stroke, traumatic brain injury and aging// Curr. Med. Chem.- 2008.- Vol.15,№4.- P.404-414
11. Levy A.P., Friedenberg P., Lotan R., et al. The Effect of Vitamin Therapy on the Progression of Coronary Artery Atherosclerosis Varies by Haptoglobin Type in Postmenopausal Women //Diabetes Care.– 2004.–Vol. 27.–P. 925–930.
12. Steinberg D., Witztum J.L. Is the Oxidative Modification Hypothesis Relevant to Human Atherosclerosis? Do the Antioxidant Trials Conducted to Date Refute the Hypothesis? //Circulation.– 2002.– Vol. 105.– P. 2107–2111.
13. Wong C.H. , Crack P. J. Modulation of neuroinflamation and vascular response by oxidative stress following cerebral ischemia- reperfusion injury // Curr. Med. Chem.- 2008.- Vol. 15, №1.- P.1-14.



healty vagotonia sympathicotony ayton

Figure.1 **Redox status of adolescents with different types of autonomic regulation**

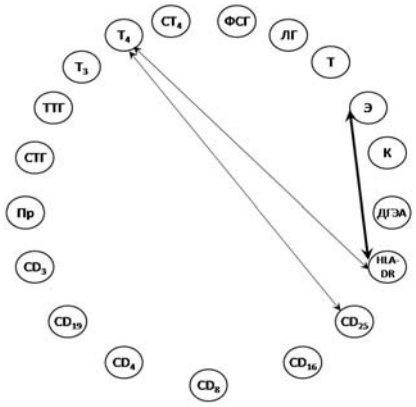
Table

Some indicators of immune status of children with SVD (M±m)

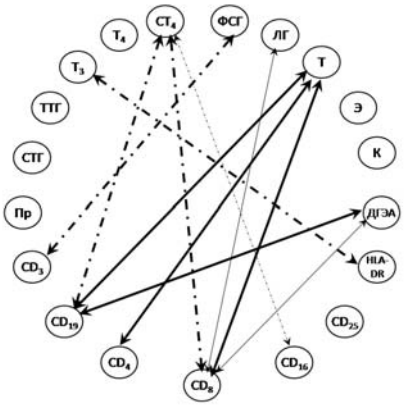
Indicator	Vagotonic type n=109	Sympathic type n=40	Atony type n=20	Control (healthy) n=78
Limph., %	46,02±1,03*	45,4±1,69*	47,91±3,08*	40,58±1,35
CD3+, %	28,49±0,93*	28,72±1,47*	25,4±3,26*	37,37±1,45
CD4+, %	23,38±0,71*	23,08±1,29*	24,0±1,59	27,27±1,02
CD16+, %	17,56±0,76*	15,0±0,88	19,55±1,17*	14,22±0,64
HLA-DR+,%	16,2±0,54*	14,25±0,79	18,0±2,9*	12,86±0,55
Limph., abs	2,72±0,08*	2,76±0,11*	3,28±0,39*	2,39±0,09
CD3+, abs	0,77±0,03*	0,79±0,05	0,9±0,16	0,89±0,05
CD16+, abs	0,47±0,02*	0,41±0,03*	0,62±0,06*	0,33±0,02
CD25+, абс	0,41±0,02*	0,39±0,04	0,54±0,14*	0,3±0,02
HLA-DR+,abs	0,44±0,02*	0,39±0,03*	0,55±0,07*	0,31±0,02
IgG, г/л	14,73±0,98*	14,65±1,12*	14,37±1,8*	20,2±1,5
IgE, МЕ/мl	171,93±23,45*	147,76±32,53*	57,0±16,65*	85,31±24,97
NSTsp, conv.un.	22,3±1,08*	24,95±2,96	22,0±1,43*	46,05±2,93
НСТ ст,conv.un.	30,51±1,3*	35,1±2,93	30,18±2,25*	55,19±2,65
FAN sp, %	32,47±1,41*	40,28±3,24*	31,73±5,39*	48,2±3,97
FAN st, %	39,06±1,48*	43,92±3,25*	45,73±6,69*	56,24±3,77

Note: * - significant differences (p<0,05) with control group indicators;

Girls



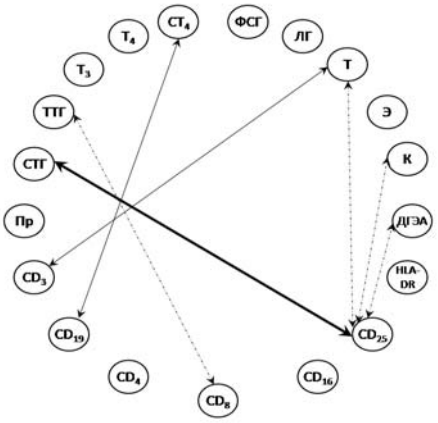
1



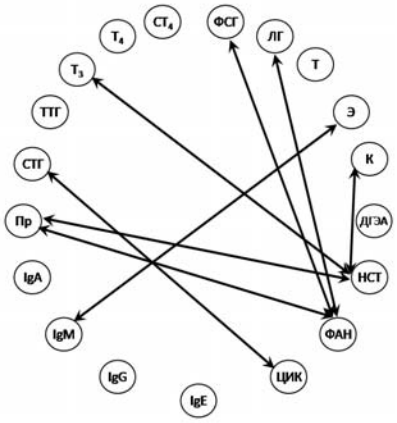
2

.

Boys



1.



2

Figure.2. **The nature of the immune endocrine relations among girls and boys with SVD in prepubertal (1) and pubertal (2) age**