

## **DEPENDENCE OF NEUROPSYCHOLOGICAL DEVELOPMENT OF EARLY AGE CHILDREN FROM THE FUNCTIONAL ACTIVITY OF SEROTONERGIC AND PITUITARY-THYROID SYSTEMS**

**Shlieienkova H. O.**

V. N. Karazin Kharkiv National University, Kharkiv, Ukraine

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The high frequency of neurological disorders in children deprived of parental care was demonstrated ( $94.1 \pm 2.2$  %). The most commonly the syndrome of statokinetic, mental and pre-speaking retardation was diagnosed ( $49.2 \pm 4.7$  %,  $p < 0,001$ ). High frequency disturbances of mental development and neurological status are accompanied by a reduction in the functional activity of the pituitary-thyroid system and the activation of serotonin. Between levels of thyrotropin and serotonin in the blood serum there is a moderate direct correlation ( $\rho = 0,56$ ), which may indicate the adaptive increasing of the serotonin system activity, designed to compensate the lack of thyroid effects.

**KEY WORDS:** neurologic status; psychological development, pituitary-thyroid system; serotonin, young children

## **ЗАЛЕЖНІСТЬ НЕРВОВО-ПСИХІЧНОГО РОЗВИТКУ ДІТЕЙ РАНЬОГО ВІКУ ВІД ФУНКЦІОНАЛЬНОЇ АКТИВНОСТІ СЕРОТОНІНЕРГІЧНОЇ ТА ГІПОФІЗАРНО-ТИРЕОЇДНОЇ СИСТЕМ**

**Шлеєнкова Г. О.**

Харківський національний університет імені В. Н. Каразіна, м. Харків, Україна

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У статті продемонстрована висока частота клінічних проявів перинатальних уражень нервової системи серед дітей раннього віку, позбавлених батьківського піклування ( $94,1 \pm 2,2$  %). Встановлено, що в структурі неврологічних порушень домінує синдром затримки стато-кінетичного, психічного і предмовленневого розвитку ( $49,2 \pm 4,7$  %,  $p < 0,001$ ). Висока частота порушень нервово-психічного розвитку та неврологічного статусу супроводжується зниженням функціональної активності гіпофізарно-тиреоїдної системи та активізацією серотонінергічної. Між рівнями тиреотропіну та серотоніну в сироватці крові існує прямий кореляційний зв'язок помірного ступеню ( $\rho = 0,56$ ), що може вказувати на адаптаційний характер підвищення активності серотонінергічної системи, спрямований на компенсацію недостатності тиреоїдних впливів.

**КЛЮЧОВІ СЛОВА:** неврологічний статус; нервово-психічний розвиток; гіпофізарно-тиреоїдна система; серотонін, діти раннього віку

## **ЗАВИСИМОСТЬ НЕРВНО-ПСИХИЧЕСКОГО РАЗВИТИЯ ДЕТЕЙ РАННЕГО ВОЗРАСТА ОТ ФУНКЦИОНАЛЬНОЙ АКТИВНОСТИ СЕРОТОНИНЕРГИЧЕСКОЙ И ГИПОФИЗАРНО-ТИРЕОИДНОЙ СИСТЕМ**

**Шлеєнкова А. А.**

Харьковский национальный университет имени В. Н. Каразина, г. Харьков, Украина

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В статье продемонстрирована высокая частота клинических проявлений перинатальных поражений нервной системы среди детей раннего возраста, лишенных родительской опеки ( $94,1 \pm 2,2$  %). Установлено, что в структуре неврологических нарушений доминирует синдром задержки стато-кинетического, психического и предречевого развития ( $49,2 \pm 4,7$  %,  $p < 0,001$ ). Высокая частота нарушений нервно-психического развития и неврологического статуса сопровождается снижением функциональной активности гипофизарно-тиреоидной системы и активизацией серотонинергической. Между уровнями тиреотропина и серотонина в сыворотке крови существует прямая корреляционная связь умеренной степени ( $\rho = 0,56$ ), что может указывать на адаптационный характер повышения активности серотонинергической системы, направленный на компенсацию недостаточности тиреоидных воздействий.

**КЛЮЧЕВЫЕ СЛОВА:** неврологический статус; нервно-психическое развитие; гипоталамо-гипофизарно-тиреоидная система; серотонин, дети раннего возраста

## INTRODUCTION

Neuropsychological development and neurological status of the young child depends on many factors that affect the nervous tissue both in utero and after birth. One of the main conditions for correct formation of the structures of the central nervous system (CNS) and provides their functional activity is an adequate level of thyroid hormones. It is believed that thyroid hormones (TH) play a role of a kind «timer», which provides a clear sequence in the formation, maturation and functioning of the nervous system. The most critical is a violation of thyroid homeostasis during the antenatal period and the first years of life. In the embryonic period of development TH affect the processes of neurogenesis, neuronal migration, maturation of axons and participate in the growth of dendrites [1–2]. Adequate levels of these hormones after birth is required for ensure timely myelination and the formation of a sufficient number of synaptic connections, a high level of functional activity of the brain [3–4].

Significant place in the regulation of the formation and functioning of the CNS also belongs to biogenic amines, particularly serotonin. Serotonin (5-hidroksitryptamin) is formed in the body as a result of conversion of the amino acid L-tryptophan in various organs and tissues. In the embryonic period, like thyroid hormones, it affects glia proliferation, differentiation of neurons, myelination of axons and accelerates the maturation of the nervous system. With its participation in the early neonatal period occurs branching of neurons. In addition, at any age serotonin acts as a neurotransmitter of synaptic transmission of nerve impulses. Mediator the role of it was first proved by V. V. Brodie and P. A. Shore (1957). Serotonin which is synthesized by specific system of neurons, moves on axons, reaching its terminals and by releasing interacts with serotonergic receptors of other neurons. The basic amount of neurons that synthesize serotonin located in nine-seam cores (nuclei raphe) and placed in the center of the middle and medulla oblongata. These neurons and their axons are regarded as specific serotonergic system of the brain. The two main serotonergic ways are described: mesolimbic and mesostriatal.

Serotonergic system of the brain is involved in regulating the overall activity level of CNS, cycles of sleep and vivacity, outdoor activity, emotional behavior, learning and memory processes.

Functioning of serotonergic and pituitary-thyroid system (PTS) is in close relationship. Back in the 60s of last century it was suggested the important role of mastocytoid serotonin in the synthesis of TH. During conducted studies it was found that tissue basophils of TG not synthesize serotonin but by it holding regulates the level of bioamines in an environment of follicles. The nature of serotonergic regulation of thyroid function depends on the actions of a mediator. It has been demonstrated that the presence of serotonin in the incubation environment provides similar to thyroid-stimulating hormone (TSH) direct stimulatory effect on thyrocytes and increases its sensitivity to TSH. In addition, it was shown that serotonin stimulates proliferation of thyrocytes by activation of anabolic processes through guanylate cyclase mechanisms of cellular regulation. In its turn, the exchange of bioamines in the brain is sensitive to changes in thyroid status: in hyperthyroidism content of serotonin in the brain tissue is usually increased, while hypothyroidism contrary - is reduced. Thus, neurotransmitters are modified of thyroidin production, on the other hand - the synthesis of neurotransmitters is controlled by TG. [5–6].

The prevalence of neuropsychological disorders and perinatal CNS dysfunction in young children has increased significantly in recent years. Group of special risk are children who arrive for life to baby home because mostly born from pregnancies that were unwanted, against the background of insufficient and/or poor nutrition, alcohol abuse, mothers smoking, without necessary medical supervision. These children often have congenital malformations, lagging in physical and neuro-psychological development. In addition, at the time of admission for the life to baby home is usually impossible to set completely anamnesis and identify specific factors of nervous system damaging. This necessitates to the study of neurohormonal disorders that affect the functional activity of CNS in young children for rationale and

develop new and improve existing rehabilitation.

## **OBJECTIVE**

The research goal is to examine functional activity of serotonergic and pituitary-thyroid system and analyze its impact on neuro-mental development and neurological status of young children.

## **MATERIALS AND METHODS**

During the study were examined 123 children aged between 2 and 3.5 months, which came for life to the baby house as children deprived of parental care (continuous pooled sample). The study was carried out after obtaining the views of Ethics Committee, the consent of the local authorities and fiduciary. After excluding children with congenital anomalies of development (5/123, 4,1 ± 1,7 %) under the supervision was remained 118 children: 56 girls (47,5 ± 4,6 %) and 62 boys (52,5 ± 4,6 %). The amount of primary research has been standardized for each child and includes: review and objective examination of children for signs of violations of the functioning of the endocrine and nervous systems and adaptive processes; assess their neuropsychological development; studying the functional level of the pituitary-thyroid and stress limits systems.

Evaluation of physical and psychomotor development of children was held in dynamics according to clinical protocols of medical care for a healthy child under 3 years approved by the Ministry of Health of Ukraine from 20.03.2008 № 149.

Evaluation of neurological status was performed based on neurological examination according to the classification of lesions of the nervous system in children and adolescents (Martynyuk V. Y.). Prevailing of clinical syndromes of the nervous system, such as the syndrome of increased neuro-reflex excitability, syndrome of statokinetic and psycho-speaking delay and syndrome of movement disorders were taken into account.

In order to examine characteristics of the functional state of the pituitary-thyroid system and its relationship with the state of stress limits system for all children was conducted in-depth research on the biochemical definition of thyrotropin (TSH).

TSH level was determined by competitive solid phase chemiluminescent enzyme

immunoassay using test kits «Immulite 1000 Rapid TSN», «Immulite 1000 Total T3» on automatic analyzer («Diagnostic Products Corporation», Los Angeles, USA).

Under the optimal functional state of the pituitary-thyroid system was considered TSH level within 0,4–2,0 mU/L with normal level of thyroxine. Increased TSH within 2,0–4,0 mU/L with normal rate of free T4 was used the term minimal thyroid dysfunction. If the TSH level was higher than 4,0 mU/L with reduction of free T4 to the lower border of norm (12,0 pmol/L) was noted the status of subclinical hypothyroidism. If level of TSH was reduced to 0,3 mU/L with higher level of thyroxine above 22,0 pmol/L was set state of hyperthyroidism [7].

The concentration of serotonin in the blood serum was determined by competitive solid phase chemiluminescent enzyme immunoassay using a set of test systems Serotonin ELISA («IBL Hamburg», Germany).

Mathematical processing was performed by variation statistics (statistical hypothesis testing, variance and correlation analysis) by which was defined qualitative and quantitative relationship between parameters of study.

Averages of arithmetic mean (M), median (Me), mode (Mo), standard error of mean values (m), standard deviation ( $\sigma$ ) and confidence intervals (CI) were calculated.

Before comparing averages and reliability assessment of differences between them was behaved verify compliance with normal Gaussian distribution. Then control of variances data was performed by Fisher criterion - in the case of normal distribution, by criterion Siegel-Tukey – in the case of abnormal distribution. In the normal distribution average data was presented in the form of  $M \pm m$  (CI 95), where the CI – confidence interval, and in the distribution, different from normal, in the form of Me [QR], where QR – interquartile range.

If the variance were equal was used t-Student test for equal variances – for normal distribution of data, the criterion of Mann-Whitney-Wilcoxon – on abnormal distribution. If the variance were unequal was used t-Student test for unequal variances – in the case of normal distribution data and Mann-Whitney two-tailed test – in the case of abnormal distribution.

In conducting the statistical analysis of qualitative variables for comparing equity parts (proportions P) was used z-criterion and

criterion  $\chi^2$  for contingency table with correction for continuity by Yates. The standard error of the difference and its 95-th confidence interval were determined.

To investigate the relationship between quantitative traits was used mated Pearson correlation coefficient ( $r$ ) in normal distribution of values and Spearman coefficient ( $\rho$ ) – in distribution of values different from normal.

Under significance level ( $\alpha$ ) during comparing statistical hypotheses was taken likelihood of rejecting the null hypothesis when it accuracy is 5 % ( $\alpha = 0,05$ ). In comparing of two values the difference between its was considered reliable at the achieved level of  $p < 0,05$ . In processing the results of the study was a used standard tool of Microsoft Excel 2007 and application package Statistica 7.0.

### RESULTS AND DISCUSSION

According to the results of the clinical neurological examination  $94,1 \pm 2,2$  % (111/118) of children had symptoms of perinatal lesions of the nervous system.

According to the data from medical staff of baby home  $45,7 \pm 4,5$  % (54/118) children had a bad dream. On examination in  $19,5 \pm 3,6$  % (23/118) of persons was observed muscular dystonia,  $21,2 \pm 3,7$  % (25/118) had an increased muscle tone, at  $4,2 \pm 1,7$  % (5/118) was occurred muscular hypotonia. Marbling of skin at the examination was observed in  $22,8 \pm 3,8$  % (27/118), recurrent spitting up in  $16,1 \pm 3,3$  % (19/118), positive symptom of Graefe in  $10,2 \pm 2,7$  % (12/118), spontaneous reflex of Moro  $16,1 \pm 3,3$  % (19/118), tremor in limbs and chin in  $58,5 \pm 4,5$  % (69/118), convergent strabismus in  $16,1 \pm 3,3$  % (19/118), nystagmus in  $3,4 \pm 1,6$  % (4/118). Increased of tendon reflexes were observed in  $45,7 \pm 4,5$  % (54/118), reduction of tendon reflexes was in  $24,6 \pm 3,9$  % (29/118) of children, reduced the amount of active and passive movements was observed in  $11,0 \pm 2,8$  % (13/118), an increased amount of active and passive movements were in  $10,2 \pm 2,7$  % (12/118) inmates of baby home (Fig.1).

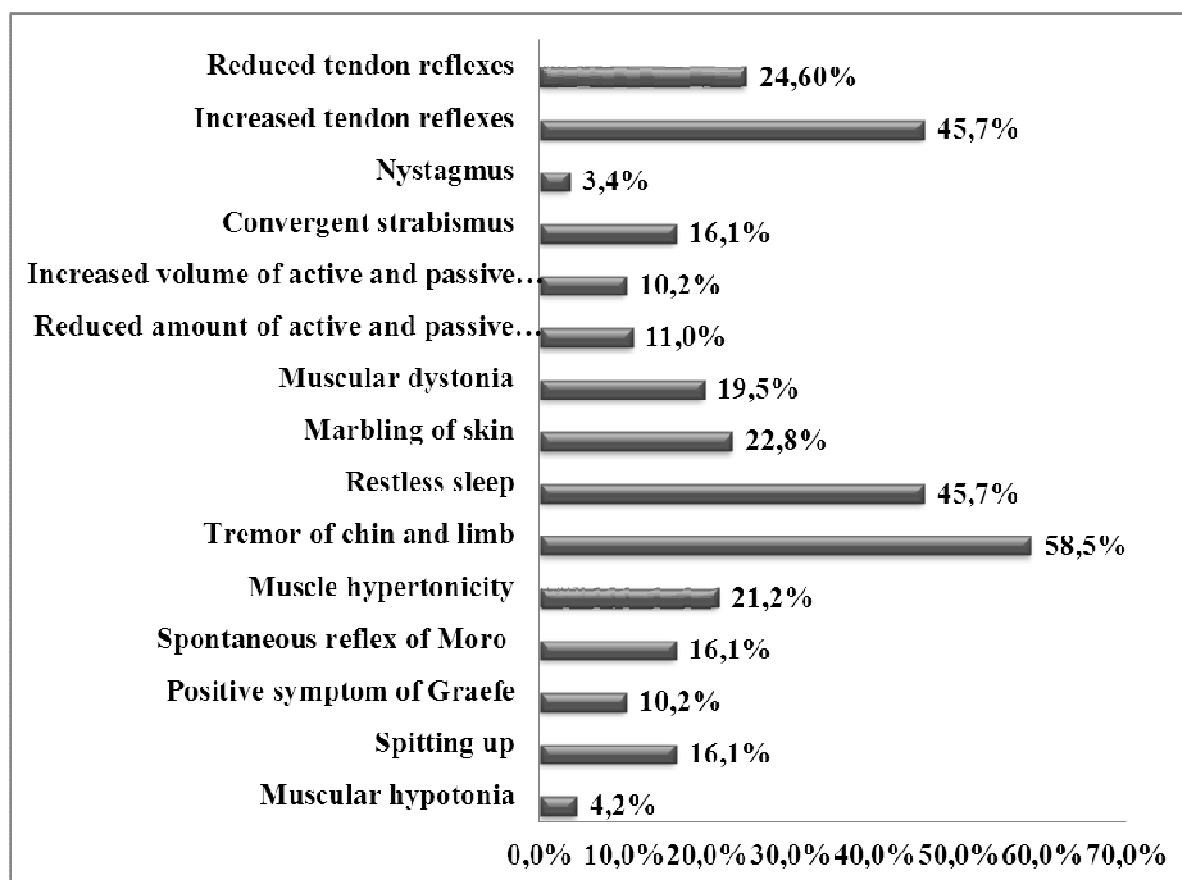
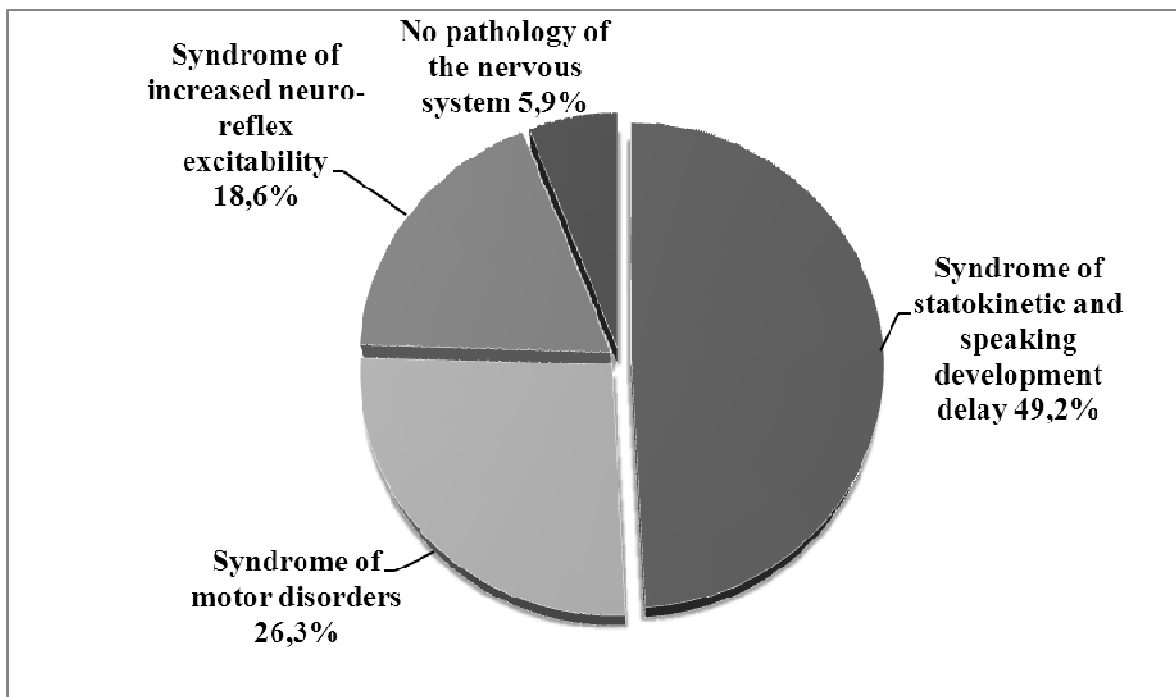


Fig. 1. The nature and frequency of the nervous system lesions in young children

In the structure of neurological disorders of the recovery period syndrome of statokinetic, mental and speaking delay was dominated. Its features were found in  $49,2 \pm 4,7\%$  (58/118) of surveyed children. The syndrome of motor disorders occurred in  $26,3 \pm 4,1\%$  (31/118,

$p < 0,001$ ) children. Manifestations of the syndrome of increased neuro-reflex excitability observed in  $18,6 \pm 3,6\%$  (22/118) of cases ( $p < 0,001$ ). No violations of CNS was found only in  $5,9 \pm 2,2\%$  (7/118) of surveyed children in baby home (Fig. 2).



**Fig. 2. Structure of neurological disorders of inmates of baby home**

Exploring of the functional state of the pituitary-thyroid axis in surveyed children allowed to establish that TSH level in blood serum, optimal range for formation of structures of CNS is 0,3–2,0 mU/L, was determined only in  $28,8 \pm 4,1\%$  (34/118) of cases. The most common indicators of TSH were in the range of 2,0–4,0 mU/L in  $44,1 \pm 4,5\%$  (52/118) of patients. The level of thyrotropin in blood serum was exaggerated more than 4,0 mU/L in  $27,1 \pm 4,1\%$  (32/118) of children. No cases of congenital or transient hypothyroidism (TSH more than 20 mU/L) were found.

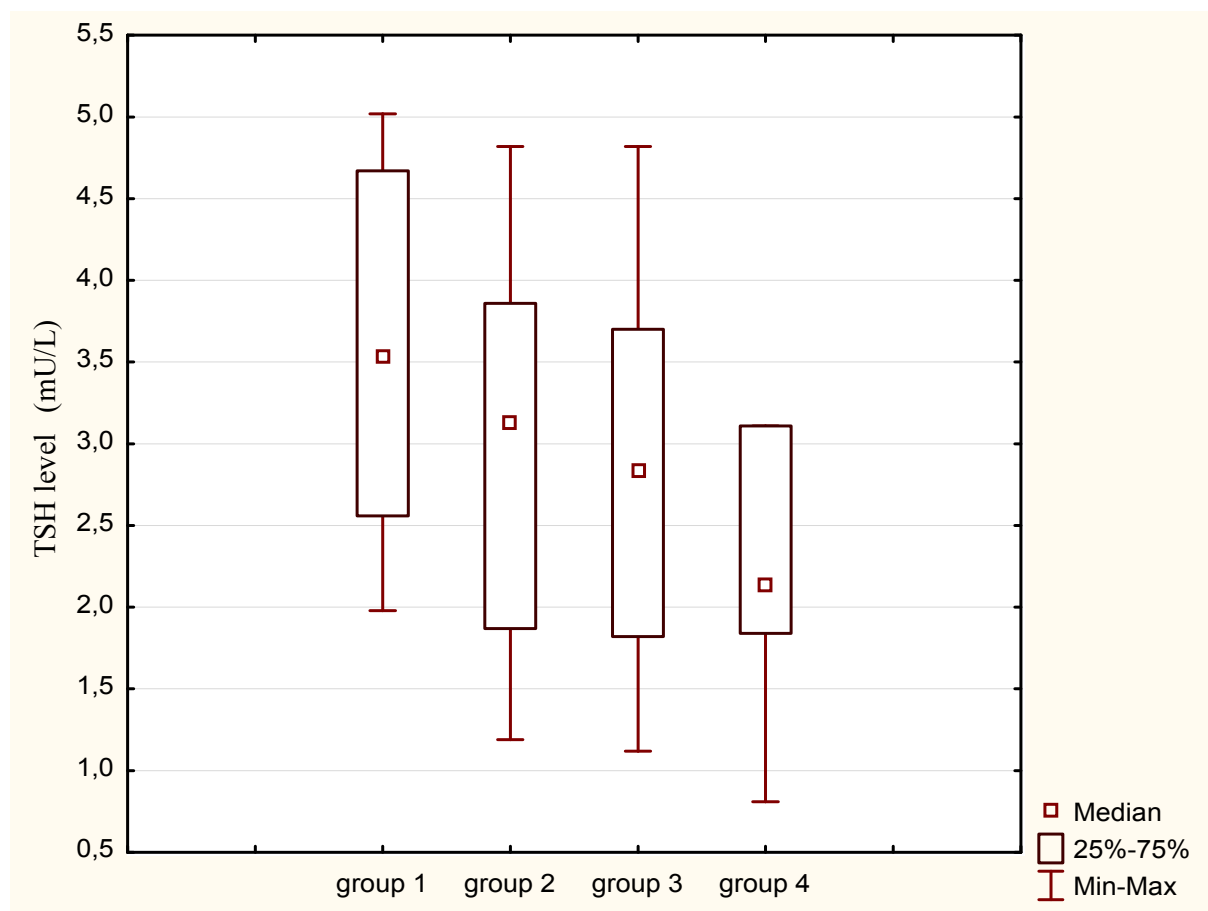
Increased of TSH more than 4,0 mU/L statistically more frequently observed in children with clinical manifestations of the syndrome of statokinetic and speaking development delayed - in  $39,6 \pm 6,3\%$  (23/58) against  $19,3 \pm 7,1\%$  (6/31) of persons with signs of syndrome of motor disorders ( $p = 0,087$ ) and  $13,5 \pm 7,2\%$  (3/22) – in children

with symptoms of the syndrome of increased neuro-reflex excitability ( $p = 0,051$ ). In the group of children with the syndrome of statokinetic and speaking delay the thyrotropin median was 3,5 mU/L [QR: 2,6; 4,7] versus 3,1 mU/L [QR: 1,9; 3,9] in children with the syndrome of motor disorders ( $p = 0,076$ ), 2,8 mU/L [QR: 1,8; 3,7] – in patients with a syndrome of increased neuro-reflex excitability ( $p = 0,697$ ) and 2,1 mU/L [QR 1,8; 3,1] – in children with no signs of disorders of the nervous system functioning ( $p = 0,637$ ) (Fig. 3).

Clinically in children with levels of TSH more than 4,0 mU/L significantly more frequently than in inmates with indices of thyrotropin within 0,3–2,0 mU/L and TSH within 2,0–4,0 mU/L were observed changing of motor features: in  $59,3 \pm 8,6\%$  (19/32) of cases versus  $5,8 \pm 4,0\%$  (2/34,  $p < 0,001$ ) and  $13,5 \pm 4,6\%$  (7/52,  $p < 0,001$ ), respectively. Facial expression and fine motor skills was

broken in children with high TSH values in  $43,7 \pm 8,6\%$  (14/32) of cases compared with patients with optimal values of thyrotropin ( $8,7 \pm 4,7\%$ , 3/34,  $p = 0,003$ ) and normal high

levels of TSH ( $9,5 \pm 4,0\%$ , 5/52,  $p = 0,001$ ). The frequency of disturbances in emotional and volitional spheres had no difference statistically.



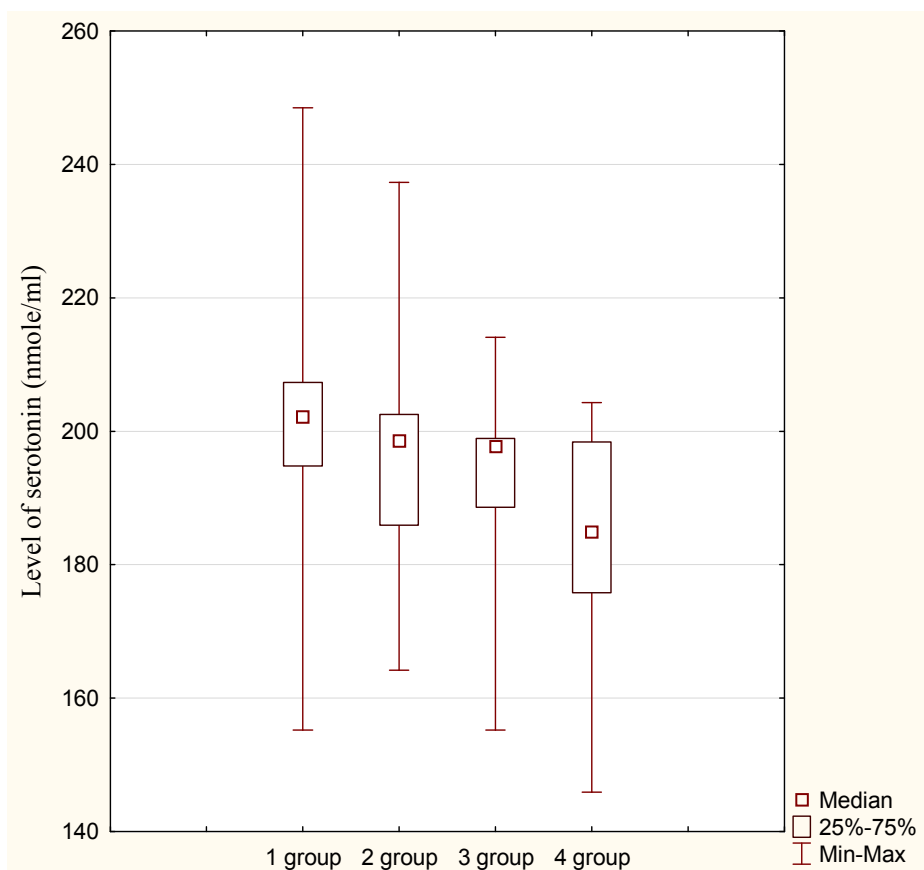
**Fig. 3. TSH level in children of early age depending on the nature of the clinical manifestations of the nervous system lesions (mU/L)**

*Notes: group 1 - children with the syndrome of statokinetic and speaking development delay; group 2 - children with the syndrome of motor disorders; group 3 - children with the syndrome of increased neuro-reflex excitability; group 4 - children without neurological disorders.*

The level of serotonin in the blood serum of children with impaired functioning of the nervous system was higher than in healthy children. In the group of children with the syndrome of statokinetic and speaking delay median of serotonin was 202,2 nmol/ml [QR: 194,8; 207,3] versus 198,6 nmol/ml [QR: 185,9; 202,5] in children with the syndrome of motor disorders ( $p = 0,025$ ), 197,7 nmol/ml [QR: 188,6; 198,9] in patients with the

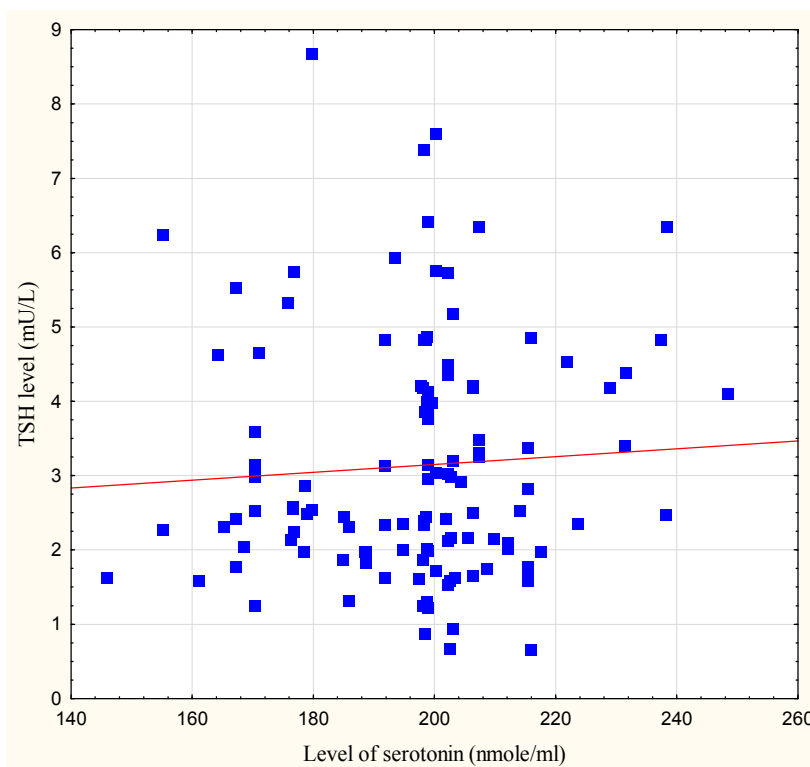
syndrome of increased neuro-reflex excitability ( $p = 0,004$ ) and 184,9 nmol/ml [QR 175,8; 198,4] – in children without signs of CNS lesions ( $p = 0,049$ ) (Fig. 4).

During carrying out of Spearman analysis correlation between TSH level and level of serotonin in blood serum was found moderately expressed direct correlation ( $p = 0,56$ ,  $p < 0,001$ ) (Fig. 5).



**Fig. 4. The level of serotonin in children of early age depending on the nature of clinical manifestations of nervous system lesions**

Notes: group 1 – children with the syndrome of statokinetic and speaking development delay; group 2 – children with the syndrome of motor disorders; group 3 – children with the syndrome of increased neuro-reflex excitability; group 4 – children without neurological disorders.



**Fig. 5. Correlation between TSH level and level of serotonin**

Therefore in the studies were detected unidirectional upward changes of TSH and serotonin in children of early age with impaired neurological status and neuropsychological development. An increased level of TSH reflects the intense functional state of the pituitary-thyroid system and, as it's known, are the results of hypothyroid periods [8–10]. The latter may be a consequence of insufficient activity of the thyroid gland, hypothalamus and pituitary gland and special requirements for thyroid hormones production that, in conditions of iodine insufficiency, debilitating thyroid gland. Hypothyreosis, in the opinion of many researchers, should be considered as one of the main factors of forming disturbances of the nervous system structures [11].

Increasing the concentration of serotonin in the blood serum of children with clinical manifestations of perinatal nervous system indicates activation of adaptive systems, aimed at launching of dendritic branching, activation of synapse formation and continuing formation of neuronal connections. Perhaps that way the child's body tries to compensate for the lack of thyroid regulation of these processes. In favor of this opinion was shown that a serotonin level

in children with impaired neurological status is higher than that of children without signs of thyroid disease.

## CONCLUSIONS

In the baby home inmates there is a high frequency of decrease of functional activity of the pituitary-thyroid system and serotonergic activation that is accompanied by neuropsychological development and neurological status lesions. Between levels of serotonin and thyrotropin in blood serum there is a moderate degree direct correlation ( $\rho = 0,56$ ), which may indicate the adaptive nature of increased activity of serotonergic systems because of thyroid deficiency.

## PROSPECTS FOR FUTURE STUDIES

It is necessary to continue further study of this problem for the development of new, more advanced methods of rehabilitation and treatment of neuropsychiatric disorders of children of early age by correction of thyroid regulation based on the study of functional features of stress limits and pituitary-thyroid system.

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