



## Features of Endocrine and Immune Status in Adolescents with Vegetative Dystonia Syndrome



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### Abstract

An assessment of the immune and endocrine statuses of 243 adolescents of puberty with vegetative dystonia syndrome (VDS), who were examined in the Youth Center of Tashkent city, was carried out, depending on gender and the presence of perinatal pathology of the nervous system (PPS) in the anamnesis. The features of hormonal regulation in adolescents with SVD with a history of PPNS were established, contributing to the progression of SVD, arterial hypertension, a high frequency of psychosomatic disorders, violations of the physical and sexual development of adolescents. The revealed changes indicate a high tension of the adaptive homeostatic mechanisms in SVD against the background of PPNS.

### Keywords

adolescents;  
dystonia;  
endocrine status;  
immune;  
nervous system;  
perinatal pathology;  
syndrome;

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## 1 Introduction

It is known that autonomic disorders are decisive in the occurrence of a breakdown of adaptation-compensatory processes, the formation of organic somatoform disorders with the involvement of almost all organs and systems in the pathological process (Alimova, 2008; Krapivkin AI & Klyuchnikov, 2009). The last decade has been characterized by an unusually intensive study of the mechanisms of interaction between the neuroendocrine and immune systems (Babichev, 2013; Kusumajaya, 2021). Evidence has been obtained indicating the presence of bidirectional communication between the neuroendocrine and immune systems, and data on the possibilities of endocrine regulation of immunogenetic are summarized in the neuroendocrine theory (Kvetnoy et al., 2003). By this theory, the realization of genetically determined capabilities of immunocompetent organs and cells is carried out under the active influence of hormones. The study of the parameters of the immune system, as well as the immunoendocrine correlations in adolescents, is of scientific and practical interest since it has the ultimate goal not only to detect patterns in the development of the immune system but also to adequately assess and predict the health status of children during mass prenosological examinations. The results obtained will help to identify the relationship between the activity of various links of the endocrine system and the state of humoral and cellular immunity (Stroyev, 2004).

Neuroimmunoregulatory relationships are fundamental in maintaining immunological defense processes and in transmitting immunity to offspring. Numerous studies have established and proven the relationship between the endocrine and immune systems. These systems use similar ligands and receptors to maintain the physiological scheme of intra- and intersystem connections, which play a decisive role in maintaining homeostasis. The concept of joint mutually directed regulation of the body's neuroendocrine-immune adaptive response to stress has ample experimental evidence. The quality and intensity of this coordinated stress response varies with age, gender, reproductive status, and other genetically determined factors, as well as the types and severity of environmental exposure. These factors and the dysfunctional connection between the nervous, endocrine, and immune systems may contribute to the formation and development of pathological conditions (Baranov et al., 2003; Belyaeva, 2011; Carchi et al., 2021). The health of adolescents depends on the state of neuroendocrine processes, immune defense it is known about the regulatory role of environmental factors and living conditions on the formation of adaptive reactions.

## 2 Materials and Methods

To study the features of the endocrine and immune status of adolescents with autonomic dystonia syndrome, depending on the transferred perinatal pathology of the nervous system. An assessment of the immune and endocrine status of 243 adolescents of puberty with vegetative dystonia syndrome (SVD) was carried out, who were examined at the Youth Center of Tashkent city in the period 2018-2020. Of these, there were 87 adolescent boys, average age  $15.0 \pm 2.2$  years, and adolescent girls 156, average age  $15.3 \pm 2.6$  years. In the course of the study, groups of adolescents with SVD were formed depending on gender and a history of perinatal nervous system pathology (PPNS), group 1 consisted of 53 (21.8%) adolescent boys with PPNS, group 2 - 34 (14.0%) adolescent boys without PPNS, 3 groups comprised 107 (44.0%), adolescent girls, with PPNS and group 4 - 49 (20.2%) adolescent girls without PPNS (Mostoufi-Zadeh et al., 1985; Pekmezovic et al., 2009).

Hormonal status included determination of the levels of hormones of the pituitary gland, thyroid gland, adrenal glands gonads by ELISA method, using test systems: Alkor-Bio, Hema (Russia). The assessment of the immune status included the determination of the parameters of the cellular link of immunity (the method of rosette formation using monoclonal antibodies (MCAT): CD3 +, CD19 +; CD4 +, CD8 +; CD16 +, CD25 +; HLA-

DR+. The indices of the humoral link of immunity (serum immunoglobulins IgA, IgM, IgG), the study of the cytokine status (IL17, Int.10, MCP A-TNF, VEGF, IL4) were carried out by the method of enzyme-linked immunosorbent assay (ELISA) using test systems ("Protein contour", St. Petersburg, and "Vector-Best", Novosibirsk). The content of circulating immune complexes (CIC) in blood serum was determined according to the standard method using polyethylene glycol. The indicators of the functional activity of neutrophils (FAN: spontaneous and stimulated) were studied in tests of phagocytic activity with the determination of the phagocytic index and phagocytic number (PN - spontaneous and stimulated) with latex particles and in the reactions of reduction of nitro-blue tetrazolium (NBT - spontaneous and stimulated, "Reacomplex", Chita). The results obtained were processed as follows: calculation of the mean, standard deviation, Mann-Whitney U-test, correlation analysis (Stroyev & Churilov, 2004; Gruenwald & Minh, 1961). Programs used: Microsoft Office Excel, Stadia.

### 3 Results and Discussions

It should be noted the high incidence of thyroid pathology, which reached 34.9% in the group of adolescents with SVD with a history of PPNS (Jankovic, 2006; LeDoux, 2012; Klein, 2014). Deviations in thyroid status with a high frequency were accompanied by a violation of the rate of formation of secondary sexual characteristics in both gender groups (14% of boys and 8% of girls). In 4% of boys and 10% of girls, sexual development occurred at a high rate, the sexual formula reached the maximum point score, however, paraclinical examination (ultrasound) revealed in them the formation of cystic-proliferative changes in the gonads (cysts of the epididymis, polyfollicular ovaries). In most of these cases, diffuse non-toxic goiter I and II degree (WHO) (22.2%), nodular goiter (6.3%), autoimmune thyroiditis (6.3%) were diagnosed. In general, in comparison of adolescents with SVD without PPNS in anamnesis and adolescents with SVD with PPNS in history, the latter showed significant thyroid dysfunction in the form of a significant decrease in TSH levels ( $1.39 \pm 0.05$  and  $1.51 \pm 0.09 \mu\text{U} / \text{ml}$  respectively) ( $p < 0.05$ ) and a significant increase in the levels of the biologically active fraction of thyroxine - FF4 ( $14.8 \pm 0.3$  and  $13.1 \pm 0.6 \text{ pmol} / \text{l}$ , respectively).

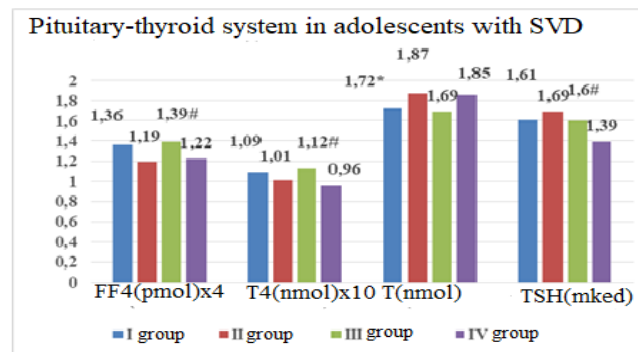


Figure 1. Pituitary-thyroid system in adolescents with SVD  
 Note: \* -  $p < 0.05$  - in groups I and II, # -  $p < 0.05$  in groups III and IV.  
 (FF4 - free fraction T4, T4 - thyroxine, T3 - triiodothyronine,  
 TSH - thyroid-stimulating hormone).

In groups I and III, the content of T3 in the blood decreases ( $1.72$  and  $1.69$ , respectively  $\text{nmol} / \text{l}$ ) and TSH ( $1.61 \pm 0.2$  and  $1.6 \pm 0.04 \text{ nmol} / \text{l}$ , respectively  $p < 0.05$ ) against the background of an increase in the levels of T4 ( $109.7 \pm 0.3$  and  $112.2 \pm 1.24 \text{ nmol} / \text{L}$ ) and CT4 ( $13.6 \pm 0.51$  and  $13.9 \pm 1.2 \text{ pmol} / \text{L}$ , respectively.) (fig. 1). The revealed changes indicate a decrease in the processes of deiodination of thyroxine, against the background of an increased need for active triiodothyronine in the body of adolescents with SVD with a history of PPNS. Relative subclinical thyroid insufficiency is also confirmed by the clinical status of most adolescents with PPNS (78%), which is characterized by a high frequency of detection of diffuse non-toxic goiter of 1-2 degrees, changes in echostructure in the form of hyperechogenicity, and heterogeneity of the thyroid gland, increased local blood flow (Lynch et al., 2008; Wolman et al., 1994). In the course of hormonal

examination, it was found that the gonad stimulating function of the pituitary gland in adolescents with SVD and PPNS begins at a later date, in comparison with adolescents with SVD without PPNS.

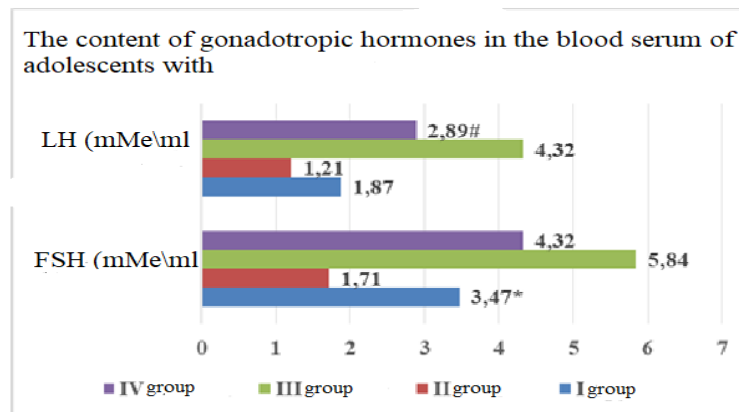


Figure 2. The content of gonadotropic hormones in the blood serum of adolescents with SVD

Note: \* -  $p < 0.05$  - in groups I and II, # -  $p < 0.05$  in groups III and IV.  
(FSH-follicle-stimulating hormone, LH-luteinizing hormone)

Significantly higher levels of FSH secretion were revealed in groups I and III ( $3.47 \pm 0.68$  and  $5.84 \pm 1.49$  mIU / ml, respectively) compared with groups II and IV ( $1.71 \pm 0.24$  and  $4.32 \pm 0.63$  mIU / ml, respectively) LGVO in groups I and III ( $1.87 \pm 0.44$  and  $4.32 \pm 0.12$  and mIU / ml) compared with groups II and IV  $1.21 \pm 0.46$  and  $2.89 \pm 0.31$  mIU / ml, respectively) ( $p < 0.005$ ). (fig. 2.) It is known that high concentrations of prolactin aggravate autonomic dysregulation, contribute to a high frequency of psychosomatic disorders, menstrual dysfunction, which occurs with a high frequency in adolescents. The revealed changes indicate a high tension of adaptive homeostatic mechanisms in SVD: the levels of prolactin in the blood serum of adolescents with SVDs PPNS do not exceed the maximum threshold norm in comparison with adolescents with SVDs without PPNS, however, on average, they are 1.2 times higher than those of adolescents without PPNS in both gender groups ( $p < 0.001$ ) (Fig. 3).

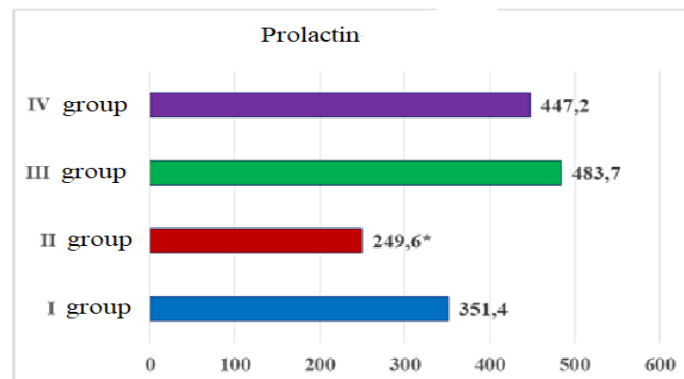


Figure 3. Serum prolactin levels in adolescents with SVD

Note: \* -  $p < 0.05$  - in groups I and II, # -  $p < 0.05$  in groups III and IV.

The functional activity of the gonads has the same tendencies: the secretion of sex hormones (estradiol - E2) in girls with SVD with a history of PPNS is significantly higher in comparison with adolescent girls with SVD without a history of PPNS ( $101.9 \pm 11.3$  and  $67.8 \pm 6.3$  pg/ml, respectively) ( $p < 0.03$ ), in boys, there were no significant differences in testosterone content, a tendency towards an increased content of E2 ( $51.4 \pm 5.6$  and  $42.1 \pm 4.9$  pg/ml, respectively) was determined, which is explained by increased aromatization in adipose tissue with metabolic disorders in adolescents with SVD.

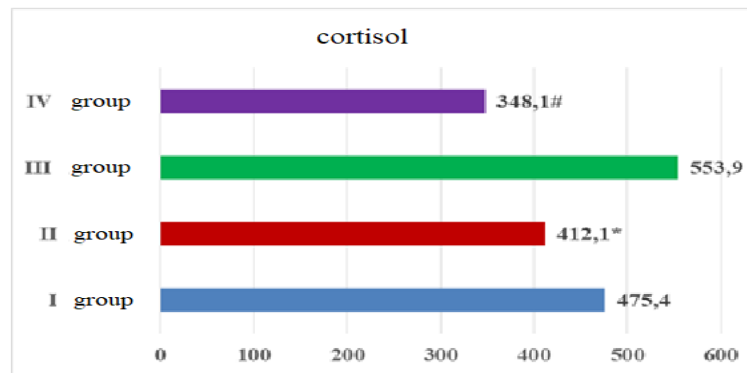


Figure 4. Blood cortisol levels in adolescents with SVD  
Note: \* -  $p < 0.05$  - in groups I and II, # -  $p < 0.05$  in groups III and IV.

When studying the secretory activity of the adrenal glands in adolescents with SVD and PPNS, high levels of cortisol are determined in comparison with adolescents with SVD without PPNS ( $p < 0.001$ ). (fig. 4).

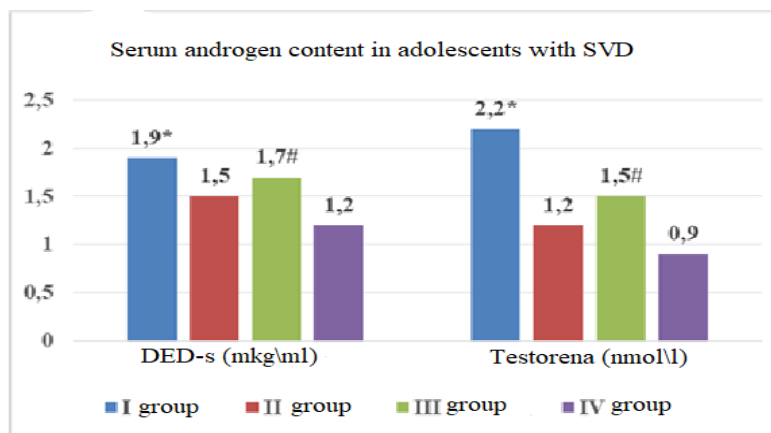


Figure 5 Serum androgen content in adolescents with SVD  
Note: \* -  $p < 0.05$  - in groups I and II, # -  $p < 0.05$  in groups III and IV.  
(DHE-c-dehydroepiandrosterone sulfate)

No reliable features of growth hormone secretion have been identified, active growth acceleration in adolescents with SVD, and history of PPNS is provided to a greater extent by the synergistic growth-stimulating effects of thyroid, adrenal, and sex hormones. Thus, the features of hormonal regulation in adolescents with SVD with a history of PPNS have been established, contributing to the progression of SVD, AH, a high frequency of psychosomatic disorders, violations of the physical and sexual development of adolescents (Zimmer-Gembeck et al., 1997; Furness, 2000). The revealed changes indicate a high tension of the adaptive homeostatic mechanisms in SVD against the background of PPNS. Comparative analysis of immunological resistance indicators in groups of adolescents with SVD, depending on the presence of PPNS in the anamnesis, showed an increase in the relative number of lymphocytes, the percentage of HLA-DR positive lymphocytes, and a decrease in the percentage of T-lymphocytes (CD3 +) in all groups of children in comparison with the normative indicators (Table 1).

An increase in the expression of the IL-2 receptor is observed in all groups of adolescents with SVD and is characterized by a significant increase in only the absolute values of CD25 + lymphocytes. The detected changes are most pronounced in adolescents in group I: the level of lymphocytosis reaches 47.4%, HLA-DR + cells - 18.3%, and CD3 + lymphocytes - 26.3%. In adolescents, II and III with the state of the cellular link of immunity are also accompanied by a decrease in the expression of CD4 + receptors of peripheral blood lymphocytes (Ranke & Saenger, 2001; Karjono et al., 2017). A significant increase in the relative number of NK

cells (CD16 +) was found in groups I and III. the absolute value of natural killers increased in all four surveyed groups of adolescents with SVD. The state of the humoral link of immunity was characterized by a decrease in IgG synthesis, the serum concentrations of which in adolescents with SVD in all groups are in the range of 14.37-14.73 g / l.

Table 1  
Indicators of the immune status of adolescents with SVD (M±σ)

Indicator	I group	II group	III group	IV group
Leukocytes, abc	6,9±0,7	6,2±0,2	6,2±0,4	6,4±0,2
Lymph., %	47,4±3,1	45,4±1,6*	46,2±1,3#	43,5±1,3
CD3+, %	26,3±3,2	28,7±1,4*	28,4±0,3#	27,7±1,5
CD19+, %	18,0±1,4	17,4±1,2	16,8±0,5	16,4±0,6
CD4+, %	24,0±1,5	23,8±1,2*	23,3±0,7#	23,7±1,2
CD8+, %	15,4±1,3*	17,2±1,2	17,5±0,7	17,9±0,7
CD16+, %	19,5±1,1*	15,0±0,8	17,5±0,7#	18,2±0,6
CD25+, %	14,9±1,83	14,8±0,9	14,9±0,2	14,8±0,6
HLA-DR+, %	18,3±2,9*	14,2±0,7	16,2±0,5#	15,6±0,5
IRI	1,6±0,1	1,4±0,1	1,5±0,05	1,43±0,05
Lymph., abc	3,2±0,3	2,7±0,1*	2,75±0,08#	2,57±0,09
CD3+, abc	0,6±0,1	0,71±0,05	0,7±0,03#	0,81±0,05
CD19+, abc	0,5±0,1	0,44±0,04	0,41±0,02#	0,46±0,02
CD4+, abc	0,7±0,1	0,62±0,04	0,67±0,02	0,65±0,03
CD8+, abc	0,56±0,09	0,47±0,04	0,48±0,02	0,45±0,02
CD16+, abc	0,62±0,06	0,41±0,03*	0,47±0,02#	0,45±0,02
CD25+, abc	0,54±0,1*	0,39±0,04	0,41±0,02#	0,39±0,02
HLA-DR+, abc	0,57±0,07	0,36±0,03*	0,44±0,02#	0,38±0,02
IgA, g / l	1,82±0,09	1,8±0,09	1,9±0,9	1,92±0,09
IgM, g / l	2,4±0,2	1,8±0,23	1,9±0,1	2,19±0,18
IgG, g / l	14,3±1,4	14,6±1,1*	14,7±0,9#	16,2±1,5
IgE, ME/ml	157,0±6,5*	147,7±12,5	171,3±14,5	185,1±13,7
CEC, conv. Units	22,5±3,5	20,8±1,9	26,3±2,4	22,5±3,3
NSTsp, conventional units	22,0±1,4*	24,9±2,9	22,3±1,08#	26,5±2,9
NST conventional ed. st,	30,1±2,2*	35,1±2,9	30,51±1,3#	35,1±2,5
FAN sp,%	31,3±5,9	40,2±3,2*	32,4±1,1#	38,2±3,9
FAN st,%	45,7±6,1	43,9±3,2*	39,6±1,4#	36,4±3,7

The immune status in group I significantly differed in the largest number of indicators from the immunological parameters of group II and was characterized by a slight decrease in the percentage of the pool of cytotoxic lymphocytes (CD8 +) and serum IgE concentration. The study of the enzymatic activity of peripheral blood lymphocytes in the test for the restoration of nitrosinegotetrazolium (NBT) revealed a decrease in the spontaneous level of cell activity in all children to 22.0-24.9 Conv. units (normal - 30.15 ± 1.07 conventional units). The phagocytic activity of neutrophils is characterized by a decrease in spontaneous and prodigiosin-stimulated indicators of functional activity of cells. In adolescents of both sexes with SVD without a history of PPNS, functional tests confirm the preservation of the phagocytic reserve by cells of the phagocytic-macrophage series, and in adolescents with SVD and with a history of PPNS, the indices of the phagocytic activity of peripheral blood neutrophils (FAN st) are reduced, but the energy potential of the cell is preserved (Chang & de Corcho, 2020; Baranov et al., 2013).



The immune status of adolescents with SVD is characterized by a decrease in the main populations of peripheral blood lymphocytes: CD3 +, CD4 +, CD8 +. In adolescent girls, an increase in the relative and absolute number of natural killer cells (CD16 +) and regulatory subpopulations of lymphocytes was revealed when compared with the immunity indices of the control group. Changes in the macrophage-monocytic system of immunity correspond to the above. Immunological indicators of adolescent boys differ from the standard values and indicators of girls by more pronounced lymphocytosis (with PPNS -  $47.4\% \pm 3.1$  and without PPNS -  $45.4\% \pm 1.6$ ), a decrease in total T-lymphocytes, a slight increase in relative values of B-lymphocytes (CD19 +) with a statistically significant increase in their absolute values. The peculiarities of the hormonal regulation of the thyroid gland function in adolescents with SVD, characterized by a decrease in the processes of thyroxine deiodination against the background of increased demand for active triiodothyronine, have been studied. Relative subclinical thyroid insufficiency is also confirmed by the clinical status of most children with SVD, which is characterized by a high frequency of detection of diffuse non-toxic goiter of 1-2 degree (WHO), changes in the form of decreased echogenicity, heterogeneity of the echostructure of the thyroid gland, and increased local blood flow. It was found that the indicators of the immune resistance of adolescents with SVD, regardless of age and sex, are characterized by changes in the parameters of the cellular, humoral links of immunity: changes in the phenotypic qualities of peripheral blood lymphocytes, modification of the ratios of effector and regulatory lymphocyte populations (CD3 +, CD4 +, CD16 +, CD25 +, HLA-DR +), a decrease in serum IgG concentration and negative dynamics of the functional characteristics of cells of the monocytic-macrophage link, which provide the first line of the body's immune defense against exogenous influences.

The dominant role in negative relationships belongs to the thyroid hormones CT4, T3. The revealed positive relationships of T3, T4, LH ( $r_{ij} = 0.36-0.49$ ) with functional indicators of immunity do not compensate for the insufficiency of the cellular link of immunity. In adolescents with SVD without PPNS, minimal interactions were determined: of the total number of significant correlation coefficients, the majority (4 positive relationships) belong to thyroid hormones - the T4 level, which positively correlates with CD25 +, HLA DR +, IgA, IgM ( $r_{ij} = 0.41-0.49$ ). In boys, the structure of immunoendocrine interactions is as follows: the degree of mutual influence of somatotropin decreases, the level of secretion of which positively correlates with CD3 +, CD8 + ( $r_{ij} = 0.36-0.42$ ), CD4 + ( $r_{ij} = 0.72$ ). A positive interaction was found between the indicators of the cellular link of immunity, testosterone and DHEA ( $r_{ij} = 0.41-0.52$ ). The average degree of activity of the influence of gonadotropins (LH, FSH, prolactin) and sex hormones in the pubertal period was established. Low activity of the phagocytic link of immunity in children with SVD and PPNS is inversely associated with an increase in FSH, testosterone in puberty.

The level of participation of cortisol and DHEA in the system of immunoendocrine relationships in SVD without PPNS is insignificant: a negative correlation was established between the level of cortisol secretion and CD25 +, CD19 + ( $r_{ij} = 0.32$  and  $r_{ij} = 0.48$ , respectively). In girls with SVD without PPNS, pituitary-thyroid hormones have a high coefficient of conjugation ( $CS = 0.24$ ) with parameters of cellular, humoral and functional immunity (CD19 +, CD3 +, CD4 +, CD25 +, HLADR +, IgE, FAN), the level of cortisol correlates in different directions with effector (CD4 +, CD16 +) and regulatory (CD25 +) pools of lymphocytes. There was a strong positive relationship of hormones with the level of T-helpers ( $r_{ij} = 0.84$ ) and a strong negative relationship with CD25 +, CD16 + ( $r_{ij} = -0.96$ ). Elevated serum DHEA-s concentrations revealed significant positive correlations in both gender groups. The contingency coefficient is low ( $KS = 0.001$ ), negatively correlated with HLADR ( $r_{ij} = -0.46$ ). The level and direction of immunoendocrine interactions in SVD with PPNS in boys does not differ from those in the group with SVD without PPNS in conjugacy, strength, and direction of connections and is characterized by a small number of significant connections.

#### 4 Conclusion

Thus, the history of immunoendocrine relationships in groups of adolescents with SVD is characterized by a low activity of intersystem interactions (the coefficients of conjugation and tightness of communication were 0.05-0.07) with equivalent participation of steroid, thyroid, and pituitary hormones in the structure of correlation Pleiades. The immunological resistance of adolescents with SVD and PPNS is characterized by changes in the parameters of the cellular, humoral links of immunity. Relative and absolute lymphocytosis, an

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increase in the total number of T-lymphocytes and natural killer cells (CD16 +), and at the same time a high level of expression of markers of late activation of blood lymphocytes (HLA-DR) is accompanied by a decrease in the indices of nonspecific defense and humoral immunity factors. The revealed disorders in the formation of the immune response at the level of the antigen-presenting stage form the insufficiency of nonspecific protective factors and require increased attention of pediatricians and immunologists for the development of immune-oriented preventive and therapeutic measures for adolescents with SVD, especially those with a history of perinatal pathology.

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