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Characteristics of Correlation Between Immunological Indicators of STH, ACTH and Cortisol in Children with Recurrent Bronchitis on the Background of Lymphatic Diathesis

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Abstract: Lymphatic diathesis in children accompanied by thymomegaly is characterized by a decrease in the body's adaptive capabilities and also contributes to the development of diseases. The state of immunity and hormonal status in children with recurrent bronchitis is a controversial issue. From this point of view, it was interesting to study the state of the immune and hormonal status in children with recurrent bronchitis against the background of lymphatic diathesis.

Keywords: recurrent bronchitis, thymomegaly, hormones, immune system, constitutional anomalies, diathesis.

The purpose of the study was to study the state of the immunological status and functional activity of the somatotropic, adrenocorticotropic functions of the pituitary gland and cortisol in sick children with recurrent bronchitis against the background of lymphatic diathesis.

Materials and methods. The survey included 119 children with RD aged 2 to 7 years. Group I included 62 (52%) patients with RB, group II included 57 (48%) patients with RB on the background of LD. Thymomegaly I degree (CTTI 0.33-0.36) was detected in 15 (26.3%) patients, II (CTTI 0.37-0.42) in 20 (35.1%) and III degree (CTTI 0.43 and more) - in 22 (38.6%) sick children. The basal levels of adenocorticotropic hormone (ACTH), somatotropic hormone (GH) and cortisol in the blood serum were determined. The state of cellular and humoral immunity in children with recurrent bronchitis was also studied.

Results. It was revealed that in children with LD during the period of exacerbation, RB is characterized by a sharp T-lymphocytopenia and their subpopulation, indicating functional deficiency of the thymus, and is also accompanied by a decrease in B-lymphocytes and a significant decrease in immunoglobulins IgM, IgG and a deep deficiency of IgA, which in turn has high inverse correlation with the degree of thymomegaly. In children with thymomegaly II and III degrees, a compensatory increase in cortisol levels ($P<0.001$) was established, against the

background of a significant decrease in ACTH and 2 times higher than the normative data for the level of GH, leading to an increase in immunosuppression in this category of patients.

One of the most common lesions of the lower respiratory tract is bronchitis, including recurrent bronchitis, which ranks second in the structure of morbidity in childhood after acute diseases of the upper respiratory tract with an average increase of 1‰ per year [1,2].

An analysis is being carried out on the problem of differential search for the causes leading to recurrent bronchitis in children [3].

Today, everyone knows about the leading role of the immune system in the development and course of bronchopulmonary diseases [4]. The central organ of immunopoiesis in children is the thymus gland. Based on this, pediatricians pay special attention to the enlargement of the thymus gland [5]. One of the main reasons for the development of RB in children is an unfavorable premorbid background [6,8]. Such conditions also include constitutional features, among which lymphatic diathesis (LD) is of no small importance.

It is known that the thymus gland is a "switchboard" in the interaction between the neuroendocrine and immune systems [7]. The pituitary-adrenal system plays a role in maintaining the immune status of children [7]. At the same time, the central place in this system is given to growth hormone, which also has a thymotropic effect.

The question of the state of immunity and hormonal status in children with recurrent bronchitis is still controversial. In addition, the influence of lymphatic diathesis on the development of RB has not been studied.

It has been established that in children with thymomegaly, changes in the immune system and cortisol levels can be considered as one of the factors in the pathogenetic mechanism of acute bronchopulmonary diseases [4]. However, the study of this problem is still fragmentary.

A comprehensive study of the role of the thymus gland in immune regulation, the interaction of hormones of the pituitary-adrenal system in children with RB against the background of LD will provide an opportunity for new directions in diagnosis, improvement of treatment regimens, and will also contribute to the prognosis of the disease in this category of patients.

Purpose of the study: to study the state of the immunological status and functional activity of the somatotropic, adrenocorticotropic functions of the pituitary gland and adrenal cortex in sick children with recurrent bronchitis against the background of lymphatic diathesis.

Materials and methods: 119 children with RD aged from 2 to 7 years were under our supervision. The average age of the examined patients was 4.1±0.82 years. The diagnosis of RB was established on the basis of clinical and radiological criteria confirmed in ICD 10 (J40.0). The diagnosis of LD was made on the basis of clinical, laboratory and radiological studies.

RB was verified on the basis of pathognomonic, clinical manifestations of the disease - complaints (low-grade fever, cough, diffuse dry and variable moist rales in the lungs), a careful collected history of the child's life and illness (repeated episodes of acute bronchitis 2-3 times or more during the year against the background acute respiratory infection) and radiological data (changes in the pulmonary pattern in the absence of infiltrative and focal shadows in the lungs). All patients were divided into 2 groups: Group I included 62 (52%) patients with RB, of which 35 (56%) were boys and 27 (34%) were girls. Group II included 57 (48%) patients with RB on the background of LD: 42 (74%) boys and 15 (26%) girls.

In patients of the second group, during the initial examination, attention was paid to the external signs of LD, the condition of the thymus and peripheral lymphoid organs. In 48 (84.2%) patients, pastous habitus was noted, which was usually noted from birth. In 35 (61.4%) patients, birth weight was high, with excessive weight and length gain during the first year of life. In patients with RB against the background of LD, thymomegaly was detected in 45 (79%) patients. The degree of thymomegaly was determined by assessing the size of the thymus gland on a chest

radiograph based on the value of the cardio-thymic-thoracic index: the ratio of the width of the thymus to the width of the chest at the level of the domes of the diaphragm.

Thymomegaly I degree (CTTI 0.33-0.36) was detected in 10 (22.3%) patients, II (CTTI 0.37-0.42) in 18 (40%) and III degree (CTTI 0, 43 and more) - in 17 (37.7%) sick children. At the same time, an increase in the right lobe of the gland was observed in 12 (26.66%), the left lobe in 19 (42.22%), and in 14 (31.11%) patients, bilateral enlargement of the thymus gland was observed.

To clarify the role of the pituitary-adrenal cortex in the regulation of the immune response, the basal level of adenocorticotropic hormone (ACTH), somatotropic hormone (GH) and cortisol in the blood serum was determined by enzyme-linked immunosorbent assay using standard kits from Human (Germany).

The number of circulating T-lymphocytes was assessed by the method of spontaneous rosette formation according to Jondal et.al., (1972). Determination of T-lymphocytes, T-suppressors, T-helpers and B-rosette-forming lymphocytes (in reaction with mouse erythrocytes) was carried out according to I.V. Ponyakina and K.A. Lebedev (1983). Quantitative determination of the concentration of immunoglobulins of the main classes IgG, IgA, IgM, IgE was carried out using a set of reagents for highly sensitive enzyme-linked immunosorbent determination of immunoglobulins in blood serum of Vector Best LLC (Novosibirsk, Russia), using the enzyme-linked immunosorbent assay method. The study was conducted at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan. Laboratory of immunology of reproduction.

Research results. As a result of immunological studies, a more pronounced suppression of the T-cell immunity in children of the Republic of Belarus against the background of LHD was established than in the group of children of the Republic of Belarus without LHD (40.5±1.18% and 48.4±0.96%, respectively) ($p< 0.001$). The average percentage of leukocytes and lymphocytes was statistically significantly higher as thymomegaly progressed than in LD children without thymomegaly and in healthy children. The average values of T-lymphocytes and their regulatory subpopulations were lower in LD children with thymomegaly than in LD children without thymomegaly, as well as in healthy children. It should be noted that a direct correlation has been identified between the degree of thymomegaly and the number of leukocytes, lymphocytes ($r=+0.71$; $r=+0.64$), as well as an inverse correlation between the degree of thymomegaly and the number of T-lymphocytes and their subpopulations ($r =-0.78$; $r =-0.68$; $r =-0.61$). Table 1.

Table 1. Characteristics of correlations between immunity indicators and the degree of thymomegaly

Indicators	LD without thymomegaly	LD with thymomegaly	
		I degree	II-III degree
Leukocytes	+0,233	+0,269	+0,71
Lymphocytes	+0,222	+0,293	+0,64
CD3+, %.	-0,304	-0,419	-0,78
CD3+CD8+	-0,201	-0,365	-0,61
CD3+CD4+	-0,336	-0,48	-0,68
Ig A	-0,25	-0,352	- 0,69

The relative content of T-helper cells had a clear tendency to decrease in patients of both groups compared to healthy children ($p<0.001$). A significant decrease in CD4+ content was noted in children of group II (29.7±0.92%) in contrast to patients in group I (32.75±1.28%, $p<0.01$). The CD8+ content in the blood of patients in both groups was reduced compared to the values of children in the control group ($p<0.01$). At the same time, the greatest decrease in CD8+ was detected in patients of group II (20.63±0.51% versus 23.75±0.51% in children of group I, $p<0.001$).

When comparing changes in the components of immunity with the degree of thymomegaly, we found a decrease in the relative number of all types of T-lymphocytes, as well as CD8+, as thymomegaly progresses. As is known [35; 36-43c.], CD8+ is a subpopulation marker and is expressed in humans on mature T lymphocytes. A significant decrease in the CD8+ count in children of group II is probably associated with a decrease in mature T-lymphocytes.

The quantitative imbalance of CD4+ and CD8+ cells led to a change in the immunoregulatory index in patients of both groups, in whom the immunoregulatory index was 1.45±0.04 µl and 1.37±0.08 µl compared to healthy children ($p < 0.05$).

In patients of group II, in contrast to patients of group I, there was a significant decrease in the CD4+/CD8+ index ($p < 0.01$).

In general, all the data presented above give the idea that in patients with RB against the background of LD, the immunoregulatory function of T-lymphocytes is more reduced compared to patients with RB.

When analyzing the CD16+ content, we found a significant increase in this indicator in patients with RB against the background of LD compared to controls ($p<0.01$); in patients with RB, the content of CD16+ did not differ statistically significantly from similar indicators in the healthy group.

Thus, the greatest decrease in the relative content of T-lymphocytes in patients of group II with lymphatic diathesis is associated with a weakening of the migration of T-cells from the thymus to the peripheral part of the immune system, i.e., in these children the processes of differentiation of T-lymphocytes are weakened.

Analyzing the B-cell component of immunity and the humoral component based on the content of immunoglobulins, we found a significant decrease in B-lymphocytes in patients of group II, while in patients of group I there was a tendency to increase B-lymphocytes.

To characterize the humoral component of immunity, an analysis of the content of immunoglobulins in the blood serum of the examined children was carried out 2.

Table 2. Indicators of humoral immunity in the studied children with RB.

№	Indicators	Conditionally healthy children n = 39	Recurrent bronchitis Group I n = 62	Recurrent bronchitis due to LD Group II n =57
1	Ig A (pg/ml)	1,04±0,05	0,58±0,064***	0,37±0,048***
2	Ig M (pg/ml)	1,13±0,04	1,83±0,08***	0,95±0,05***
3	Ig G (pg/ml)	10,77±0,63	11,4±0,41	8,87±0,38*
4	Ig E (pg/ml)	30,6±2,3	42,6±2,4***	36,8±1,9*

*Note: * - differences relative to the data from the healthy group are significant (* - P<0.05, ** - P<0.01, *** - P<0.001)*

In sick children in group I, an increase in IgM levels was found during the period of exacerbation of the disease compared to healthy children ($P<0.05$), which indicates the presence of an infectious agent. Whereas, the level of IgM was significantly low in patients of group II and amounted to 0.95±0.05 pg/ml, which apparently indicates the inability of B-lymphocytes to adequately respond to an infectious agent in children against the background of LD associated with the immaturity of these cells, and as a result, the inability to produce immunoglobulins.

When comparing changes in the level of IgM with the degree of thymomegaly, we found a more pronounced decrease in grade III thymomegaly 0.82 ± 0.065 pg/ml, while in grade I they corresponded to the normative indicators of 1.11 ± 0.06 pg/ml, in grade II there was a downward trend compared to the group of healthy children (1.03±0.07 pg/ml versus 1.13±0.04 pg/ml).

When studying the concentration of IgA in the blood serum of patients in group I, there was a

significant decrease in the content of IgA compared to the control group, which indicates a decrease in the body's humoral defense. But lower IgA content was found in group II patients. Thus, in patients of group II, the IgA level was 2.8 times lower than the normative data (P<0.001). Also, we identified an inverse correlation (-0.69) between the level of Ig A and the degree of thymomegaly. If in children in group II with grade I thymomegaly the Ig A content was 0.54±0.084 pg/ml, then in children with grade II-III thymomegaly it was 0.35±0.06 pg/ml (P<0. 05).

The study of Ig G content in the studied groups of patients revealed that its change in children with RB was not significantly significant and only tended to increase.

In children in the RB group with LD, there was a significant decrease in IgG levels, respectively 11.4±0.41 pg/ml and 8.87±0.38 pg/ml (p<0.05). A decrease in serum IgG levels in children of group II may be associated with both a disruption in the process of switching the synthesis of IgG isotypes and a disruption in the formation of memory B cells.

IgE levels were high in patients of both groups (p<0.05). At the same time, in patients of the second group with grade II-III thymomegaly, the level of IgE was more elevated compared to healthy children, respectively 44.7±2.3 pg/ml and 30.6±2.3 pg/ml (p<0. 05).

Thus, it was revealed that in the children with RB we studied, the immune response to the infectious agent was insufficient and was characterized by either the development of excessive-hyperergic or infectious syndrome of secondary immunodeficiency, in which case allergic syndrome of secondary immunodeficiency develops. Our study showed a combination of these syndromes often in patients with RB against the background of LD.

The above indicates that with RB in children, dysregulation of both the cellular and humoral components of the immune response as a whole is observed.

In order to assess the functional state of the pituitary-adrenal cortex system in children with RB and RB against the background of LD, we examined 119 sick children aged 2 to 7 years. The first group consisted of 62 patients with RB and the second group of 57 patients with RB against the background of LD. Test

The group consisted of 39 practically healthy children of the same age.

The results of studies of hormone content are presented in table. 3.

Table 3. Basal level of ACTH, STH, cortisol in patients without exacerbation of the disease (M±m)

Indicators	Conditionally healthy children n=39	Recurrent bronchitis n=62	Recurrent bronchitis due to LD n=57
STH ng/ml	1,83±0,21	2,95 ± 0,41**	2,02±0,19
ACTH pmol/l	12,2±2,31	12,9±2,21	6,7±2,31*
Cortisol ng/ml	210±15,91	185±14,82	215±16,71

Note: * - differences

Note: * - differences relative to the data from the healthy group are significant (* - P<0.05, ** - P<0.01, *** - P<0.001)

As can be seen from Table 3, the basal level of GH in healthy children aged 2-7 years was 1.83±0.21 ng/ml, ACTH 12.2±2.31 pmol/l and cortisol level was 210±15.91 ng/ml.

When studying the relationship in healthy children, the level of growth hormone correlates to a moderate degree with T-helpers, IgM and IgG negatively, and B-lymphocytes and T-suppressors with a positive relationship. There is a negative relationship between cortisol and growth hormone (Table 3).

Table 4. Correlation relationships between STH, ACTH and cortisol between immunological parameters in healthy children 2-7 years old.

Indicators	STH	ACTH	Cortisol
CD3+	+0,014	+0,15	-0,347
CD4+	-0,44	+0,054	+0,373
CD8+	+0,19	+0,098	-0,247
CD19+	+0,24	+0,18	-0,21
IgA	-0,03	-0,48	+0,3
IgM	-0,4	-0,57	+0,087
IgG	-0,31	-0,23	+0,67
ACTH			-0,59
STH			-0, 47

Pituitary ACTH correlates with low B-lymphocyte levels (+0.18) and has an inverse relationship with cortisol and three classes of immunoglobulins. Positive correlative connections have been established between cortisol and two classes of Ig A and M in healthy children.

In general, the maintenance of a certain level of T-lymphocytes is facilitated by the physiological concentration of cortisol, and to a lesser extent by ACTH; T-helpers are inversely related to the level of growth hormone; and T-suppressors - from the level of cortisol. The level of immunoglobulins is directly dependent on the concentration of cortisol and inversely dependent on ACTH and STH. Under physiological conditions, there are negative relationships between cortisol and ACTH, as well as cortisol and GH, which help maintain the integrated interaction of the endocrine and immune systems in children.

The results of studies of hormone levels in the patients we studied showed that during the period of remission there was a slight increase in the concentration of cortisol and growth hormone and an almost twofold decrease in ACTH in children of the second group. The ACTH/cortisol ratio decreased by almost half and amounted to 0.031 versus 0.058 in healthy people.

In patients of group II during the period of exacerbation of the disease, a higher level of growth hormone (5.13±0.79 ng/ml) and a low value of ACTH (5.33±1.37 pmol/l) were revealed with an unreliable decrease in the level of cortisol (170.9± 10.36 nmol/l). A comparative assessment of the content of cortisol, ACTH and GH depending on the degree of enlargement of the thymus gland revealed that in children with thymomegaly II-III there was an increase in cortisol levels to 316±24.6 nmol/l, a more significant decrease in ACTH (5.12±1. 21pmol/l) and a GH level 2 times higher than the normative data (4.02±0.4 ng/ml). The ACTH/cortisol ratio was only 0.016, which is 2.4 times lower than the physiological figure.

As is known, steroid hormones weaken the production of thymulin, inhibit the synthesis of specific antibodies and inhibit the migration of lymphocytes from the intravenous fluid [5]. This fact was confirmed in our study, i.e. in patients with RB with stage II-III thymomegaly, an increased level of cortisol during an exacerbation of the disease led to an increase in immunodeficiency.

Table 5 Basal levels of ACTH, STH, cortisol in patients with exacerbations of the disease (M±m)

Indicators	Conditionally healthy children n=39	Recurrent bronchitis n=62	Recurrent bronchitis due to LD n=57
STH ng/ml	1,83±0,21	1,21 ± 0,41	5,13±0,79 ***
ACTH pmol/l	12,2±2,31	20,2±4,9	5,33±1,37 **
Cortisol ng/ml	210±15,91	367±15,28***	170,9±10.36

Note: * - differences Note: * - differences relative to the data from the healthy group are significant (* - P<0.05, ** - P<0.01, *** - P<0.001)

Data analyzes show that in children of group II, cooperative connections in the ACTH/cortisol, ACTH/GH, and GH/cortisol systems are disrupted, as evidenced by not an inverse, but a direct correlation between their levels, as well as a weakening or disappearance of the correlation between them Table 6.

Table 6 Correlations of cortisol between ACTH, GH and immunological parameters.

Indicators	Healthy children	Group I	Group II
CD3+	-0,347	-0,275	-0,37
CD4+	+0,373	-0,26	-0,13
CD8+	-0,247	-0,43	-0,21
IgA	+0,3	-0,32	-0,16
IgM	+0,087	+0,37	+0,05
IgG	+0,67	+0,17	-0,11
ACTH	-0,59	+0,57	+0,35
STH	-0, 47	-0,28	+0,019

Thus, the identified correlations in children indicate the presence of tension in the pituitary-adrenal system in children of group II and changes the correlation relationship with immunity indicators.

In patients of group I, it was found that the level of ACTH (20.2±4.9 pmol/l, $p < 0.05$) and cortisol in the blood plasma (367±15.28 ng/ml $p < 0.01$) during the exacerbation period RB significantly increased compared to healthy children, with subsequent normalization of ACTH during the period of remission of the disease, despite the absence of changes in cortisol levels. It should be noted that in the group of children who received systemic glucocorticosteroids immediately before admission to the hospital, a sharp decrease in cortisol levels was found (85.4±28.7ng/ml, $p<0.001$), probably associated with the depletion of the functional capacity of the adrenal cortex due to its suppression functions by the entry of exogenous hormone into the body. In non-exacerbation of the disease, a tendency towards normalization of cortisol levels was noted, but it did not reach the values obtained in the control group of practically healthy children.

Thus, the results of our studies give reason to believe that during the period of exacerbation of the disease, considered as stress of the body in response to a pathogen, the level of ACTH compensatory increases, which in turn stimulates the production of cortisol, however, the feedback principle does not work sufficiently in the patients we studied . During the period of remission of RB, due to an increase in the affinity of the transcortin protein for cortisol, the level of free hormone decreases, and although the level of total cortisol remains elevated, the feedback mechanism begins to be fully realized.

Analysis of data from a study on the level of GH in the blood plasma in children with RB group I during the period of exacerbation was slightly low, amounting to 1.21 ± 0.41 ng/ml compared with indicators in healthy children 1.83 ± 0.21 ng/ ml. While the level of this hormone during the period of remission of the disease turned out to be slightly increased and amounted to 2.95 ± 0.41 ng/ml

Thus, changes in immunological reactivity in children of group II reduce the morphofunctional properties of the body's immune and endocrine systems for adaptation to environmental influences and can lead to relapses of diseases and immunopathological reactions.

Conclusion.

Recurrent bronchitis in children with LD during the period of exacerbation is characterized by worsening insufficiency of the immune system in these patients, manifested by severe T-lymphocytopenia and their subpopulation, indicating functional failure of the thymus, and is also accompanied by a decrease in B-lymphocytes and a significant decrease in immunoglobulins IgM, IgG and deep deficiency IgA, which in turn has a high inverse correlation with the degree of thymomegaly.

In the general group of patients with recurrent bronchitis with LD, during the period of exacerbation of the disease, high levels of growth hormone and low levels of ACTH are observed with an unreliable decrease in cortisol levels. Whereas in children with thymomegaly II, III degrees, a compensatory increase in cortisol levels ($P < 0.001$) was established, against the background of a significant decrease in ACTH and 2 times higher than the normative data for the level of GH, leading to an increase in immunosuppression in this category of patients.

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