ENDOCRINE-IMMUNOLOGICAL RELATIONSHIP IN RHEUMATOID ARTHRITIS IN CHILDREN OF DIFFERENT AGES

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Abstract*. Our study data showed that changes in immune and endocrine system parameters persist for a long time in rheumatoid arthritis. Including glucocorticoid hormones in therapy for patients with articular-visceral rheumatoid arthritis demonstrated positive dynamics in immune and endocrine system parameters. Treatment of patients with glucocorticoids only improved the course of the disease but did not eliminate the underlying disease.*

Keywords: *juvenile rheumatoid arthritis; lymphocytes; adrenocorticotropic hormone; triodothyroxine, thyroxine.*

Introduction.

Currently, rheumatoid arthritis remains one of the urgent problems of pediatric rheumatology. Rheumatoid arthritis (RA) is a progressive autoimmune disease throughout life that affects mainly the synovial joints [1]. Before the disease, there are genetic and environmental risk factors that contribute to the susceptibility to the disease, then the preclinical phase (of variable duration), where systemic autoimmunity manifests itself in the presence of autoantibodies, especially anti-citrulline peptide antibodies (ACPA), but without clinical signs of joint damage. This is followed by a phase of nonspecific symptoms, including arthralgia (joint pain), but still without signs of clinical synovitis [2,3]. Multiple genetic and environmental factors have been associated with an increased risk of developing rheumatoid arthritis (RA) [4]. The mechanism of the underlying disease includes an autoimmune attack on the articular bone and cartilage, which leads to a clinical picture of joint pain and swelling with subsequent disability and concomitant pathology. Rheumatoid arthritis (RA) is characterized by the presence of autoantibodies, such as rheumatoid factor (RF), anticyclic citrulline peptide-2 (anti-CCP2) and antibodies against carbamylated protein (anti-CarP) [5].

The nervous, endocrine and immune systems are coordinated to maintain the homeostasis of the body, generating a bi-directional connection through common mediators and receptors [6]. Meanwhile, the study of the state of the endocrine and immune systems in juvenile rheumatoid arthritis provides the information necessary for differential diagnosis, treatment tactics and prognosis of the disease. The early period of rheumatoid arthritis plays a decisive role in the development and progression of immune complex inflammation. At the same time, early diagnosis of RA allows prescribing adequate treatment and obtaining a more significant clinical effect, as well as improving the prognosis of this disease [7.8].

However, the clinical variants of rheumatoid arthritis are largely dependent on the formation of various interorgan combined lesions [9]. In this regard, cardiological, immunological, clinical relationships, and vegetovisceral dysfunctions are quite described. At the same time, to date, it is not precisely the immunological and endocrine relationships that have been studied in

this pathology. In this regard, the goal of our research was to study the relationship of immunological parameters and indicators of the endocrine system in rheumatoid arthritis in children. It was suggested that the research results will contribute to the improvement of diagnostic methods and the choice of more effective therapy in various clinical options for the course of the disease.

Materials and research methods.

The study was carried out at the bases in the cardiac rheumatology departments of the 4-city clinical children's hospital in Tashkent. A comprehensive clinical, laboratory and instrumental examination of 98 children was carried out, 58 of which were girls (59%) and 40 boys (41%) aged 7 to 17 years with juvenile juvenile disease. The duration of the JRA ranged from 6 months to 7 years. Among the patients examined by us, about half were children with a disease period of 1-3 years. Separation of children according to the forms and variants of the course of rheumatoid arthritis was carried out in accordance with the classification of juvenile rheumatoid arthritis according to ICD-10. The joint form of the disease was observed in 66 children (the maximum activity of the disease was in 19, moderate in 27, minimal in 20), articular-visceral in 32. The control group consisted of 20 healthy children of the same age. The diagnosis of rheumatoid arthritis is based on clinical, biochemical, immunological and radiological examinations.

The main drugs used to treat patients with rheumatoid arthritis were non-steroidal anti-inflammatory drugs in combination with methotrexate. With the articular-visceral form of rheumatoid arthritis, glucocorticoid hormones were included in the therapy. The immune system was evaluated by the content of T - and B - lymphocytes in the blood. In addition to these populations of lymphocytes, cells without surface markers, the so-called O-lymphocytes, were isolated. And also the level of serum immunoglobulins of classes A, M, G. Endocrine status was assessed by studying the basal level of hormones of the anterior pituitary gland (adrenocorticotropic hormone-ACTH, thyroid-stimulating hormone-TSH), thyroid gland (triiodothyroxine - T3, thyroxine - T4, adrenal cortex) . Studies were carried out in the dynamics of the pathological process when children were admitted for treatment, in the phase of convalescence upon discharge from the hospital, and in follow-up (up to 3 years).

Results and discussion

Analysis of the relative and absolute content of lymphocytes in peripheral blood in children with rheumatoid arthritis revealed a significant increase in it. The number of lymphocytes was in direct proportion to the activity and form of the disease. The quantity of T-lymphocytes in the blood was reduced. At the same time, the number of B-lymphocytes, regardless of the activity and form of rheumatoid arthritis, was higher than in children of the control group (P <0.001). The relative and absolute content of O-cells was increased with moderate and maximum activity of rheumatoid arthritis. The concentration of immunoglobulins in serum in patients with rheumatoid arthritis was higher than in children of the control group (P <O, 001). The data are presented in tables 1,2,3,4.

Table 1. Indicators of endocrine and immune status in children with rheumatoid arthritis articular form of the disease of the first degree (M±m)

Indicators	**Control group**	**First degree**	**P**
Lymphocytes	2,203 ± 0,162	2,511 ± 0,127	> 0,05
T-lymphocytes	1,424 ± 0,099	1,302 ± 0,063	> 0,05
B-lymphocytes	0,286 ± 0,092	0,894 ± 0,081	< 0,001

O-lymphocytes	0,202 ± 0,065	0,201 ± 0,061	> 0,05
TSH (IU/ml)	8,21 ± 0,71	8,03 ± 0,37	> 0,05
T_3 (nmol/l)	1,51 ± 0,08	1,39 ± 0,06	> 0,05
T_4 (nmol/l)	79,24 ± 7,25	78,60 ± 7,91	> 0,05
ACTH (nmol/l)	25,3 ± 0,88	26,91 ± 0,73	> 0,05
Cortisol (nmol/l)	496,1 ± 8,2	430,5 ± 6,9	< 0,001
IgG (IU/ml)	82,1 ± 2,9	121,1± 3,2	< 0,001
IgM (IU/ml)	129,1 ± 8,7	188,2 ± 17,6	< 0,05
IgA (IU/ml)	71,1 ± 4,2	96,5 ± 4,4	< 0,001

Note: *the table shows the absolute content of lymphocytes (x109 / l of blood); P - significance of differences in relation to the control group.*

Table 2. Endocrine and immune status indicators in children with rheumatoid arthritis articular form of the disease of the II degree (M±m)

Indicators	**Control group**	**Second degree**	**P**
Lymphocytes	2,203 ± 0,162	3,324 ± 0,237	< 0,001
T-lymphocytes	1,424 ± 0,099	1,607 ± 0,075	> 0,05
B-lymphocytes	0,286 ± 0,092	1,194 ± 0,073	< 0,001
O-lymphocytes	0,202 ± 0,065	0,496 ± 0,058	< 0,001
TSH (IU/ml)	8,21 ± 0,71	12,13 ± 0,27	< 0,001
T_3 (nmol/l)	1,51 ± 0,08	1,33 ± 0,07	< 0,05
T_4 (nmol/l)	79,24 ± 7,25	75,18 ± 4,23	> 0,05
ACTH (nmol/l)	25,3 ± 0,88	29,11 ± 0,61	< 0,001
Cortisol (nmol/l)	496,1 ± 8,2	387,9 ± 7,8	< 0,001
IgG (IU/ml)	82,1 ± 2,9	133,1± 4,2	< 0,001
IgM (IU/ml)	129,1 ± 8,7	197,1 ± 18,6	< 0,001
IgA (IU/ml)	71,1 ± 4,2	104,2 ± 6,7	< 0,001

Note: *the table shows the absolute content of lymphocytes (x109 / l of blood); P - significance of differences in relation to the control group.*

Table 3. Endocrine and immune status indicators in children with rheumatoid arthritis articular form of the disease of the III degree (M±m)

Indicators	**Control group**	**Third degree**	**P**
Lymphocytes	2,203 ± 0,162	3,401 ± 0,212	< 0,001
T-lymphocytes	1,424 ± 0,099	1,682 ± 0,071	> 0,05
B-lymphocytes	0,286 ± 0,092	1,294 ± 0,078	< 0,001
O-lymphocytes	0,202 ± 0,065	0,582 ± 0,065	< 0,001
TSH (IU/ml)	8,21 ± 0,71	13,51 ± 0,39	< 0,001
T_3 (nmol/l)	1,51 ± 0,08	1,28 ± 0,09	< 0,05
T_4 (nmol/l)	79,24 ± 7,25	61,93 ± 3,29	< 0,05
ACTH (nmol/l)	25,3 ± 0,88	30,31 ± 0,91	< 0,001
Cortisol (nmol/l)	496,1 ± 8,2	324,6 ± 8,3	< 0,001
IgG (IU/ml)	82,1 ± 2,9	151,4 ± 5,2	< 0,001
IgM (IU/ml)	129,1 ± 8,7	198,7 ± 15,3	< 0,001
IgA (IU/ml)	71,1 ± 4,2	112,7 ± 5,1	< 0,001

Note: *the table shows the absolute content of lymphocytes (x109 / l of blood); P - significance of differences in relation to the control group.*

In children with rheumatoid arthritis, there were significant changes in the endocrine system. Activation of the anterior pituitary gland occurred, which was manifested by an increase in the level of TSH and ACTH. Concentrations of cortisol, T3, and T4 were low. The content of the hormones we studied in children with rheumatoid arthritis depended on the activity and form of the disease.

Table 4. Endocrine and immune status indicators in children with rheumatoid arthritis of the articular-visceral form diseases (M ± m)

Indicators	**Control group**	**Articular-visceral form**	**P**
Lymphocytes	2,203 ± 0,162	3,401 ± 0,212	< 0,001
T-lymphocytes	1,424 ± 0,099	1,682 ± 0,071	> 0,05
B-lymphocytes	0,286 ± 0,092	1,294 ± 0,078	< 0,001
O-lymphocytes	0,202 ± 0,065	0,582 ± 0,065	< 0,001
TSH (IU/ml)	8,21 ± 0,71	13,51 ± 0,39	< 0,001
T_3 (nmol/l)	1,51 ± 0,08	1,28 ± 0,09	< 0,05
T_4 (nmol/l)	79,24 ± 7,25	61,93 ± 3,29	< 0,05
ACTH (nmol/l)	25,3 ± 0,88	30,31 ± 0,91	< 0,001
Cortisol (nmol/l)	496,1 ± 8,2	324,6 ± 8,3	< 0,001
IgG (IU/ml)	82,1 ± 2,9	151,4 ± 5,2	< 0,001
IgM (IU/ml)	129,1 ± 8,7	198,7 ± 15,3	< 0,001
IgA (IU/ml)	71,1 ± 4,2	112,7 ± 5,1	< 0,001

Note: *the table shows the absolute content of lymphocytes (x109 / l of blood); P - significance of differences in relation to the control group.*

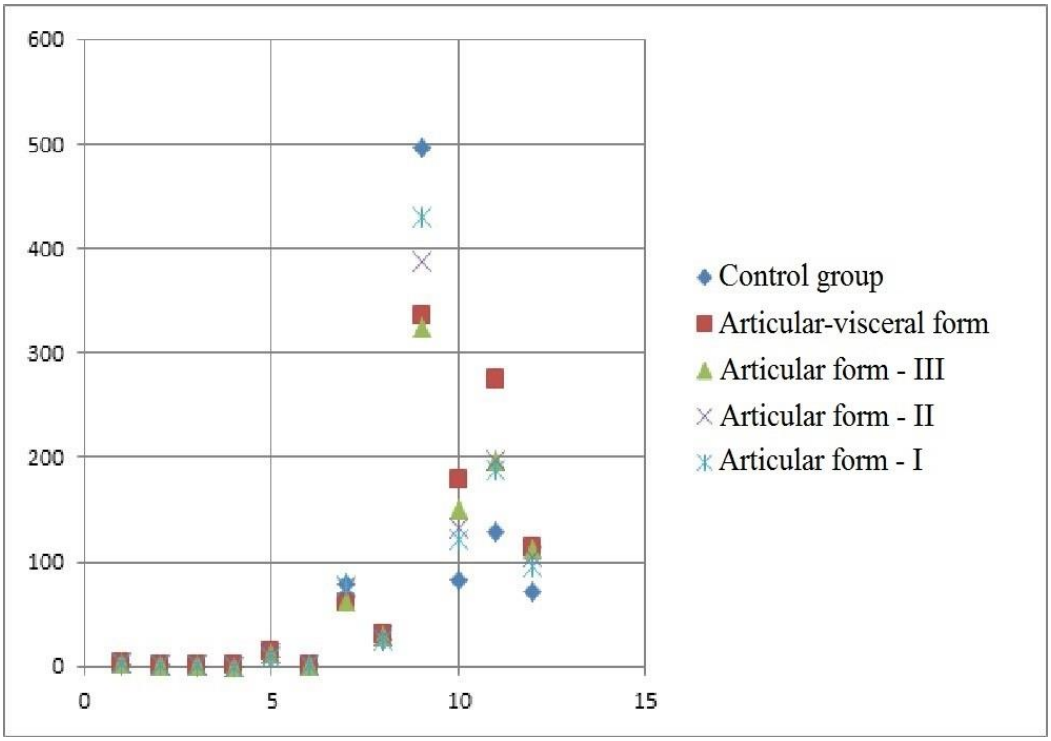


Fig. 1. Characterization of the correlation between the parameters of the endocrine system and immunity in children with rheumatoid arthritis, depending on the form

An analysis of the correlations of the studied parameters of the immune and endocrine systems (Fig. 1) showed that in the children of the control group, a moderate inverse correlation was observed between the content of T and B lymphocytes (r = -0.5694); between the concentration of TSH, ACTH and the level of T3 (r = -0.5416); T4, cortisol (r = -4654); as well as between the level of cortisol and the number of b-lymphocytes (r = -0.3988); between the concentration of the studied hormones and the content of T-lymphocytes. In addition, a moderate direct correlation between the concentration of thyroid hormones and the content of B lymphocytes (r = + 0.4955) was revealed.

In children with rheumatoid arthritis, a direct correlation was revealed between the TSH content and the number of B and O-lymphocytes (r = + 0.5049), and feedback with the number of T-lymphocytes (r = -0.3894). Inverse correlation was found between the level of T4, T3 and indicators of the immune system (r = -0.4894). The opposite relationship was found between the level of cortisol and the number of T- and B-lymphocytes (r = + 0.4956). There was revealed f direct relationship between the concentration of ACTH and the number of T-lymphocytes (r = + 0.6852), and a feedback with the number of B-lymphocytes (r = -0.5612).

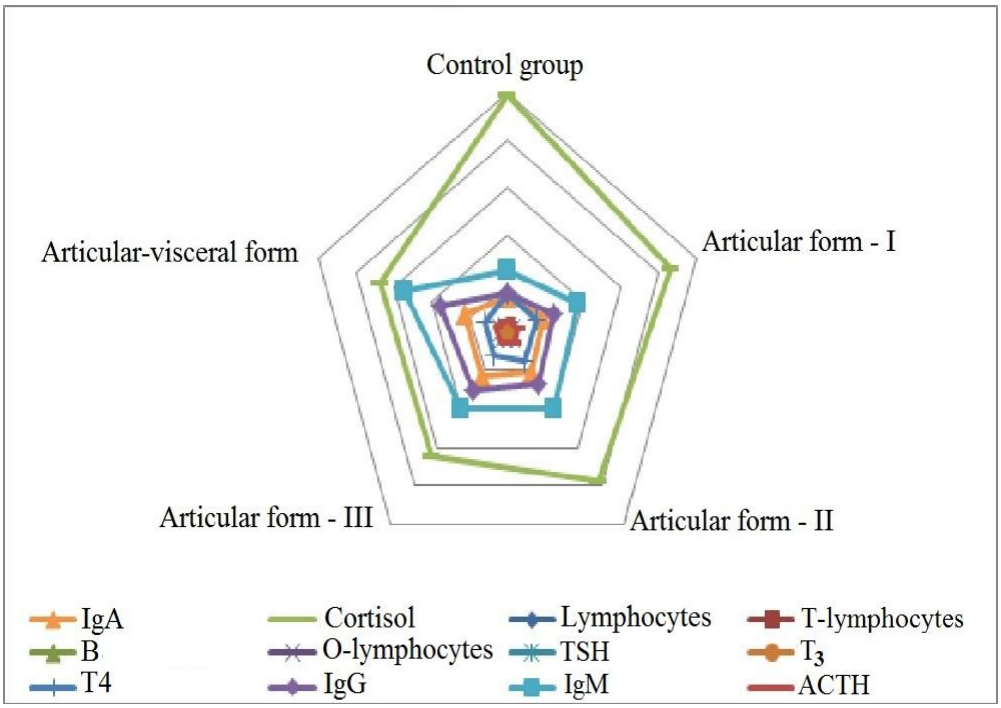


Fig. 2. Model of regulation in the space of signs of the endocrine and immune systems in healthy and rheumatoid arthritis children.

According to our data, for rheumatoid arthritis, depending on the form of the disease in children, there was a high level of TSH and ACTH and a low content of T3, T4 and cortisol. With prolonged exposure to stress, the excretion of hormones by the effector glands decreases and the level of pituitary hormones increases according to the principle of negative feedback. A similar type of endocrine system functioning was revealed by us in children with rheumatoid arthritis. There are also significant changes in the immune status: the content of T-lymphocytes in the blood decreases and the activity of the B-system of immunity increases. Activation of the B-system of immunity, apparently, is associated not only with the insufficient suppressive activity of the T-system of immunity, but also with the partial removal of the limiting effect of glucocorticoid hormones on the kinetics of lymphocytes. Depending on the severity and form of the disease, the closeness of correlations was also revealed.

Depending on the activity and form of rheumatoid arthritis, the limits of the adjustable parameters of the model were different. The more active and more severe the disease progressed, the more significantly the studied parameters differed from physiological ones. This model of regulation of the endocrine and immune systems is characteristic of a chronically ongoing process. With this type of regulation, a deep restructuring of the functioning of both the endocrine and immune systems occurs. During the period of complex therapy of the articular form of rheumatoid arthritis in children, the regulation borders in the multidimensional space of the studied symptoms shift in the opposite direction, but within very small limits. However, visually you can see, mainly the changes in the parameters are parallel, as evidenced by the positive correlation relationships (Fig. 2).

Conclusion

In children with articular-visceral rheumatoid arthritis, significant changes in parametric functions were detected, which is associated with the introduction of glucocorticoids in complex therapy and with their prolonged use. Thus, with juvenile rheumatoid arthritis, there is a deep restructuring in the functioning of the immune and endocrine systems, which is manifested by the torpidity of the course of the disease, the involvement of new joints and organs in the process.

REFERENCES

1. Пончел Ф., Бурска А.Н., Хант Л. и соавт. Аномалии подмножеств Т-клеток предсказывают прогрессирование в континууме воспалительного артрита: последствия для лечения. (*F.Ponchel, A.N. Burska, L.Hunt et al. Anomalies in subsets of T-cells predict progression in the continuum of inflammatory arthritis: consequences for treatment.*) Sci Rep 10, 3669 (2020). https://doi.org/10.1038/s41598-020-60314-w
2. Пирназарова Г. З., Тахирова Р. Н. Ферментативная активность нейтрофилов и лимфоцитов периферической крови при бронхиальной астме у детей //Молодой ученый. (*G. Z. Pirnazarova, R. N. Takhirova Enzymatic activity of neutrophils and peripheral blood lymphocytes in children with bronchial asthma // Young scientist.*) – 2016. – №. 19. – С. 172-174.
3. Тахирова Р. Н., Алимухамедова М. О. К., Огли А. А. А. Частота заболеваний 6-7-летних детей по данным госпитализации //Вопросы науки и образования. (*R. N.Takhirova, M. O. Alimuhamedova K., A. A. A. Ogli Frequency of diseases of 6-7-year-old children according to hospitalization // Issues of Science and Education.*) – 2019. – №. 3 (47).
4. E.C. de Moel, V. Derksen, L.A. Trouw, H. Bang, G. Collee, L.R. Lard, S. Ramiro, T.W.J. Huizinga, C.F. Allaart, R.E.M. Toes, et al., In rheumatoid arthritis, changes in autoantibody levels reflect intensity of immunosuppression, not subsequent treatment response, Arthritis Res. Ther. 21 (1) (2019) 28.
5. M.K. Verheul, S.J. van Erp, D. van der Woude, E.W. Levarht, M.J. Mallat, H.W. Verspaget, J. Stolk, R.E. Toes, A.E. van der Meulen-de Jong, P.S. Hiemstra, et al., Anti-carbamylated protein antibodies: a specific hallmark for rheumatoid arthritis. Comparison to conditions known for enhanced carbamylation; renal failure, smoking and chronic inflammation, Ann. Rheum. Dis. 75 (8) (2016) 1575–1576.
6. Martínez C, Juarranz Y, Gutiérrez-Cañas I, et al. A Clinical Approach for the Use of VIP Axis in Inflammatory and Autoimmune Diseases. Int J Mol Sci. 2019;21(1):65. Published 2019 Dec 20. doi:10.3390/ijms21010065
7. K.D. Deane, M.K. Demoruelle, L.B. Kelmenson, K.A. Kuhn, J.M. Norris, V.M. Holers,

Genetic and environmental risk factors for rheumatoid arthritis, Best Pract. Res. Clin. Rheumatol. 31 (1) (2017) 3–18.

8. Mankia, K. & Emery, P. Обзор: доклинический прогресс ревматоидного артрита в направлении профилактики. Артрит & . Ревматология (*Review: preclinical progress of rheumatoid arthritis towards prevention. Arthritis &. Rheumatology*) 68 , 779–788 (2016).
9. Shim, JS, Kim, C., Ryu, JJ et al. Корреляция между заболеванием суставов ТМ и ревматическими заболеваниями, обнаруженными при сцинтиграфии костей, и клиническими факторами. (*Correlation between TM joint disease and rheumatic diseases detected by bone scintigraphy and clinical factors.*) Sci Rep 10, 4547 (2020). https://doi.org/10.1038/s41598-020-60804-x