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COURSE OF GLOMERULONEPHRITIS IN CHILDREN WITH CONNECTIVE TISSUE DYPLASIA

Abstract. The clinical and laboratory features of acute glomerulonephritis in children with connective tissue dysplasia in the environmentally unfavorable Surhandarya region were studied. Multiple stigmas of connective tissue dysplasia and dysembryogenesis were more common in patients with acute glomerulonephritis with nephrotic syndrome and nephrotic syndrome with hematuria. In children with acute glomerulonephritis and multiple stigmas of connective tissue dysplasia and dysembryogenesis, pronounced and more prolonged edema, significant proteinuria was more often noted, and there were high indicators of process activity. The presence of multiple stigmas of connective tissue dysplasia and dysembryogenesis in patients with acute glomerulonephritis can be an indirect criterion for predicting the severe course of acute glomerulonephritis and the high activity of the process, which is important to consider when prescribing therapy.

Keywords: Children, glomerulonephritis, connective tissue, dysplasia, immunology.

Introduction

Connective tissue dysplasia (CTD) is a violation of the development of connective tissue in the embryonic and postnatal periods, a genetically determined condition characterized by defects in fibrous structures and the basic substance of connective tissue. Dysplastic changes in the connective tissue significantly affect homeostasis, metabolism and immunity at the tissue, organ, and body levels in the form of various morphological and functional disorders of the visceral and locomotor organs with a progressive course and determine the characteristics of the associated pathology, as well as the pharmacokinetics and pharmacodynamics of drugs [1]. Connective tissue (CT) performs numerous functions: morphogenetic, biomechanical, trophic, barrier, plastic, etc., the leading of which is the integration of various organs and tissues of the body into a single whole [2; 4]. Morphological changes in the CT itself, changes in metabolic processes, immunogenesis cause the occurrence of secondary disorders from the internal or-

gans, which often determines the severe course and prognosis of the underlying pathological process [6]. Connective tissue dysplasia syndromes (CTDS) are genetically heterogeneous, and according to several authors, they are detected with a high frequency in children with renal pathology, incl. in patients with pyelonephritis, interstitial nephritis, cystitis, nephroptosis, glomerulonephritis [3; 4; 5]. Unfavorable environmental factors leading to the formation of "secondary environmental immunodeficiency" affect the metabolism of connective tissue, the state of cell membranes, therefore, in such patients, the negative effect of connective tissue dysplasia should be more pronounced [1; 7; 8]. CTDS are manifested not only by external signs, but also by the features of the immune status with a decrease in the activity of T-lymphocytes, deficiency of CD3+, CD4+, impaired phagocytosis, changes in the level of IgA, IgM, IgG, impaired formation, and elimination of circulating immune complexes (CIC), due to a decrease in activity and intensity of macrophage-monocytic

immunity [1; 4]. This leads to the development of immunopathological and immunocomplex diseases, including acute glomerulonephritis (AGN), which has a specific clinical course.

The aim of the work was to study the clinical and laboratory features of AGN in children with connective tissue dysplasia living in the environmentally disadvantaged Surhandarya region.

Materials and research methods

We examined 94 children with AGN living in the Surhandarya region, aged from 1 to 7 years, who were treated at the Regional Children's Clinical Association and City Children's Hospital № 1. In 50 patients, AGN proceeded with nephritic syndrome, in 26 – with nephrotic syndrome (NS), in 18 – with NS and hematuria. All patients underwent a conventional clinical and laboratory examination, which included the identification of connective tissue dysplasia stigmas and dysembryogenesis. The degree of disorganization of the basic substance of the connective tissue was determined by the level of sialic acids, seromucoids, C-reactive protein, CIC.

Results and its discussion

During the examination of 94 children with AGN, CTD stigmas were detected in 84,04 ± 3,78% of patients, multiple connective tissue dysplasia stigmas (3 or more) were detected in 39,3 ± 5,04%, that is, in every third patient with AGN.

Of the connective tissue dysplasia stigmas, anomalies of the hands and feet (41.5 ± 5.08%) and flat feet (40.4 ± 5.06%) were the most common. Age spots and hypermobility of the joints occurred with the same frequency (33.9 ± 5.0%), and postural disorders, scoliosis were detected in 20.2 ± 4.14% of patients. Other connective tissue dysplasia stigmas (deformation of the chest, hernias, myopia, tall stature and long fingers, sandal gap, deformity of the gallbladder, mitral valve prolapses) occurred in less than 10% of the examined patients. More than 5 stigmas of CTD had 3 out of 94 children. The absence of CTD stigmas was found in 16.0 ± 3.8% of children with AGN. In various forms of AGN, CTD stigmas

occurred with almost the same frequency ($p > 0.05$). Three or more CTD stigmas occurred with equal frequency in patients with nephritic syndrome (39.6 ± 6.4%) and nephrotic syndrome (41.0 ± 10.7%). This may indicate that the characteristics of metabolism and immunity in children with CTD predispose to the development of AGN, but do not determine its form. Since CTD is genetically determined, the peculiarities of connective tissue metabolism can occur in utero, which affects the formation of some stigmas of dysembryogenesis. Dysembryogenesis stigmas were detected in 9.4 ± 2.9% of patients with AGN, multiple dysembryogenesis stigmas (3 or more) were detected in 51.0 ± 5.1% of children, that is, in every second patient with AGN.

Of the stigmas of dysembryogenesis, the tendency to syndactyly II, III toes were most common (78.7 ± 4.2%), with the same frequency – gothic palate and hypertelorism (respectively 56.3 ± 5.1 and 52.1 ± 5.1%), somewhat less often – deformation of the earlobes (20.2 ± 4.1%), low hair growth on the forehead (18.0 ± 3.9%). Other stigmas of dysembryogenesis, such as anomalies in the shape of the skull, epicanthus, anomalies of the kidneys, anomalies of the eyes, cryptorchidism, an additional nipple on the chest, hypertrichosis, occurred in less than 5% of the examined children. More than 5 stigmas of dysembryogenesis had 8 out of 94 children (8.5 ± 2.9%).

The incidence of dysembryogenesis stigmas in various forms of AGN had several differences. In the nephrotic form of AGN, more often than in the nephritic form, there were 3 or more dysembryogenesis stigmas, which were detected in 68.18 ± 10.2% of patients with the nephrotic form and in 41.3 ± 6.4% with the nephritic form ($p < 0,05$). At the same time, 1–2 stigmas of dysembryogenesis were more often detected in nephritic syndrome (28 patients, 48.2 ± 6.5%) and only in 5 out of 22 patients with nephrotic syndrome ($p < 0.05$). The presence of multiple dysembryogenesis stigmas in patients with nephrotic syndrome indirectly indicates a negative effect of connective tissue metabolism, membrane permeability,

immunity, its regulatory systems (cytokines) on the occurrence of nephrotic syndrome in AGN.

In isolated urinary syndrome, the incidence of dysembryogenesis stigmas did not differ from the frequency in AGN with nephritic syndrome, so these two groups of patients were not separated. The nature of dysembryogenesis stigmas in groups of patients with various forms of AGN did not differ significantly ($p > 0.05$).

The presence of a combination of CTD stigmas and dysembryogenesis was found in almost all patients with AGN ($98.9 \pm 1.0\%$). Only one child did not have CTD stigmas and dysembryogenesis. It was a boy of school age who fell ill after suffering a sore throat. AGN in this child proceeded with nephritic syndrome. Most children ($84.0 \pm 3.7\%$) had more than 3 stigmas of CTD and dysembryogenesis, only $14.9 \pm 3.6\%$ of children, mainly with AGN nephritic syndrome, had 1–2 stigmas of CTD and dysembryogenesis. No child with nephrotic syndrome had less than 3 stigmas of CTD and dysembryogenesis. At the same time, all children with nephrotic syndrome and the vast majority (13 out of 14) of children with nephrotic syndrome with hematuria had more than 3 stigmas of CTD and dysembryogenesis. The combination of more than 5 stigmas of CTD and dysembryogenesis had $54.2 \pm 5.1\%$ of patients, that is, every second patient with AGN. The presence of 5 or more stigmas of CTD and dysembryogenesis was significantly more common in nephrotic syndrome ($68.18 \pm 10.20\%$) and nephrotic syndrome with hematuria ($78.5 \pm 11.4\%$) than in nephritic syndrome ($43.1 \pm 6.5\%$, $p < 0.05$).

Thus, the presence of multiple stigmas of CTD and dysembryogenesis in a patient with AGN can be an indirect criterion for predicting a severe course of the process with damage not only to the glomerular apparatus, but also to the basement membrane. Since AGN with nephrotic syndrome and AGN with nephrotic syndrome with hematuria were more common in patients with multiple stigmas of CTD and dysembryogenesis, the clinical manifestations in these patients had certain features. Edema syndrome

in patients with AGN with CTD stigmas was more often expressed in the form of anasarca ($39.2 \pm 5.4\%$) and moderate edema ($16.4 \pm 4.1\%$, $p < 0.05$), and in children with AGN without stigma of CTD, pastosity of the eyelids and shins prevailed ($80.0 \pm 10.69\%$, $p < 0.01$). Edema was longer in patients with AGN with CTD stigmas (12.3 ± 1.0 days), and in patients without CTD stigmas, the duration of edema was 8.0 ± 1.3 days ($p > 0.05$). The number of CTD stigmas did not affect the severity of the edematous syndrome and its duration. Hypertension syndrome did not differ significantly in these groups of patients ($p > 0.05$). Gross hematuria was somewhat more common in patients with AGN without CTD stigmas ($86.70 \pm 9.08\%$, $p > 0.05$). Its duration did not depend on the presence or absence of CTD stigmas. Proteinuria up to 1 g/l was more common in patients with AGN without CTD stigmas ($73.4 \pm 11.8\%$), in patients with CTD, proteinuria more than 2 g/l prevailed ($p < 0.05$). The average level of daily proteinuria in patients with CTD stigmas was 2.6 times higher than in patients without CTD stigmas. The incidence of leukocyturia in patients with AGN did not depend on the presence of CTD ($p > 0.05$). Acute phase parameters (sialic acids, diphenylamine test, seromuroid, C-reactive protein), levels of CIC and cryoglobulins, fibrinogen were increased more significantly in patients with AGN who had CTD stigmas. This is since the presence of CTD stigmas reflects some features of the metabolism of connective tissue structures, acute phase parameters, the level of CIC and cryoglobulins, fibrinogen were analyzed depending on the presence or absence of CTD stigmas.

Thus, in patients with AGN with CTD stigmas, sialic acids were elevated in $62.8 \pm 6.77\%$ of cases, their average level was 261.0 ± 11.0 units; diphenylamine test increased in $70.5 \pm 6.3\%$, the average level of diphenylamine test was 0.290 ± 0.011 units; seromuroid was elevated in $49.02 \pm 7.0\%$ of patients, its average level was 0.32 ± 0.01 u.op.pl. In patients with AGN without CTD stigmas, sialic acids, diphenylamine test, and seromuroid were elevated only in

1/6 patients, and the average level of sialic acids was 182.5 ± 17.0 arb. units, diphenylamine test – 0.2 ± 0.01 u.p.m. ($p < 0.01$), seromuroid – 0.3 ± 0.02 op.pl. ($p < 0.001$). The average level of C-reactive protein in the presence of CTD stigmas was 4.6 times higher than in patients without CTD stigmas ($p < 0.01$). The mean fibrinogen level was somewhat higher in the presence of CTD stigmas (5.0 ± 0.3 g/l, $p > 0.05$). The number of CTD stigmas had some effect on the degree of increase in acute phase parameters, CIC, cryoglobulins, fibrinogen. In patients with multiple CTD stigmas, all these indicators were higher. Probably, more pronounced metabolic and immune changes in patients with multiple stigmas of CTD and dysembryogenesis affect the degree of connective tissue destruction in patients with AGN.

Findings

Most children with AGN have CTD and dysembryogenesis stigmas, while every third child has multiple CTD stigmas, and every second child has multiple dysembryogenesis stigmas. Significantly more often, 5 or more stigmas of CTD and dysembryogen-

esis are detected in AGN with nephrotic syndrome and AGN with nephrotic syndrome with hematuria and hypertension. In children with CTD stigmas, the edematous syndrome is more pronounced and longer, with significant proteinuria, and higher rates of process activity. Thus, the presence of multiple stigmas of CTD and dysembryogenesis, on the one hand, indicates an adverse effect in the ante- and postnatal period, predisposing to the development of AGN. On the other hand, the presence of multiple stigmas of CTD and dysembryogenesis in patients with AGN may be an indirect criterion for the severe course of AGN, the high activity of the process, which is important to consider in prognosis and therapy. Determining the stigmas of CTD and dysembryogenesis is a simple, informative method, publicly available and not difficult for a pediatrician. The study of the detection of CTD stigmas and dysembryogenesis is especially important at the present stage due to the deterioration of the environmental situation and the change in the classical clinic of the disease.

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