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The Role of Stigma of Dyzembryogenesis in the Diagnosis of Orphan Diseases in Children

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ABSTRACT:
In order to identify the role of the stigma of dysembryogenesis in the diagnosis of orphan diseases in children, data from 168 medical histories of children aged 1 to 18 years with a diagnosis of glomerulonephritis (acute-130 and chronic-38) for 2017-2021, who received inpatient treatment in a multidisciplinary children's hospital, were analyzed. ASMI clinic. It was found that currently orphan diseases in children (Alport syndrome) are underdiagnosed, and timely detection of the stigma of dysembryogenesis plays an important role in the early diagnosis of the disease. Stigmas of dysembryogenesis, such as a flattened occiput, pronounced brow ridges, hypertelorism of the eyes, epicanthus, high Gothic palate, anomaly of the auricles, hypertelorism of the nipples, chest deformation, sandal-shaped gap between 1-2 fingers of the hands and feet, clinodactyly can be considered as early phenotypic signs Alport syndrome in children.

Introduction

It is known that the global trend of increasing the number of diseases classified as rare and those suffering from such diseases indicates that the relevance of these issues will only increase and in most developed countries these issues are included in the sphere of state interests [1-5]. Currently, up to 8000 rare diseases are known in the world, and the number of patients with rare diseases is 6-8% of the total population [6-8]. More than 80% of rare diseases are based on genetic disorders, which, as a rule, manifest themselves at an early age, therefore, more than half of all patients are children, since 30% of children with orphan diseases do not live to the age of 5 [9-15].

In this regard, early detection of the stigma of dysembriogenesis of orphan diseases, including Alport syndrome, is important to expand and improve diagnostic resources.

Materials And Methods

We analyzed data from 168 medical records of children aged 1 to 18 years with a diagnosis of glomerulonephritis (GN) (acute-130 and chronic-38) for 2017-2021 who received inpatient treatment at the children's multidisciplinary clinic of ASMI.

As a control group, 30 children aged 1-18 years old suffering from non-hereditary kidney diseases were taken.

Of the examined children: nephritic variant of OGN- 84 (61.8%), nephrotic variant – 22 (16.2%) and in 30 children (22.1%) - nephrotic syndrome with hematuria and hypertension.

The nephrotic form of HCG is 31 (65.6%), the mixed form is 7 (21.4%), the

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hematuric form is 4 (11.5%). Children with orphan diseases, including Alport syndrome (persistent hematuria, hearing loss, eye damage, impaired kidney function in at least one family member) were selected from among children with acute glomerulonephritis (in 8 cases) and 4 among chronic forms of glomerulonephritis.

The total number of children with Alport syndrome accounted for all cases of acute glomerulonephritis - 6.2% and for chronic forms of this disease – 12.5%, which confirms that Alport syndrome is more registered among chronic kidney disease.

By gender, boys (75%) prevailed in the examined patients, which significantly exceeds (3:1) the proportion of girls (25.0%, $p<0.01$), which indicates the coupling with the sex X chromosome in the recessive type of inheritance.

The largest number of examined children were aged 6-10 years - 6 children (50%) and 11-14 years (41.7%), the smallest for the age period up to 5 years (8.3%).

In the study of family members of sick children, we used an integrated approach: clinical and anamnestic, laboratory (clinical and biochemical) and genealogical studies. Air and bone audiometry of the auditory threshold was also performed on a domestic audiometer.

It turned out that the identification of the stigma of dysembriogenesis is one of the important factors in the early diagnosis of the disease. A general analysis of blood, urine and feces was performed using general clinical laboratory methods. When interpreting the indicators of urine analysis, the typing of hematuria variants was carried out using the criteria West C.C. 1976, Bragon J. 1977, according to Y.Y.Illeka et al. (2000), the severity of erythrocyturia according to the recommendations of T.V.Sergeeva (1976). The digital data were processed by the method of variational statistics with the calculation of the reliability of numerical differences in the Student.

The study of the frequency of diseases in patients with Alport syndrome showed that they belong to the group of children who are often ill ($P<0.01$), at an early age they often suffered intestinal infections, hepatitis, respiratory infections (up to 4-7 times a year), the frequency of viral infections such as rubella, herpes, measles ($P<0.01$), suffered from allergic pathology ($P<0.01$), which had a statistically significant association with maternal pregnancy pathologies ($P<0.001$).

During the study, the peculiarities of the course of pregnancy and the obstetric history of mothers were studied. Mothers were more likely to suffer from pregnancy toxicosis, a history of bleeding was revealed; among extragenital diseases, pathology of the kidneys and urinary tract ($P<0.01$), cardiovascular diseases ($P<0.001$), endocrine pathologies ($P<0.01$), diseases of the gastrointestinal tract ($P<0.05$) were more often detected. Among patients with Alport syndrome, children born with low body weight (≤ 2700 gy.) prevailed when compared with the control group ($P<0.01$).

The main clinical symptoms of Alport syndrome in children were pallor, fatigue, symptoms of intoxication, pasty, headaches, hypotension, dry skin, cyanosis under the eyes, external stigmas of dysembriogenesis, renal stigmas, hearing loss and visual impairment.

The blood pressure level in patients with Alport syndrome was SAD (95.0±5.36 mmHg), DAD (58.0±1.71 mmHg) and arterial hypotension was often detected – 63.2% compared with children of the control group (24.3% and 55.4%) ($P<0.001$). In patients with chronic renal failure in the terminal stage, there was a pronounced manifestation of edematous syndrome. Urinary syndrome was manifested by persistent proteinuria – 3.66±0.78%, a decrease in daily diuresis (509±44.2 ml). Hematuria was also detected, that is, erythrocyturia amounted to 5-6 unchanged and 8-10 altered erythrocytes, leukocyturia 6-9 in the field of vision. The specific gravity of urine averaged 1010±2.75.

One of the pathognomonic symptoms of Alport syndrome is hearing loss, which is manifested by neuritis.

In our studies, audiometric evidence of hearing loss, such as grade I-II hearing loss, was detected in 6 cases (30%), clinical hearing loss in 7 cases (72.0%), which is consistent with literature data (50-60%). Cochlear neuritis was confirmed in 3 cases.

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The frequency of detection of dysembriogenesis stigma prevailed in patients with hearing loss (Fig.1,2,3,4).

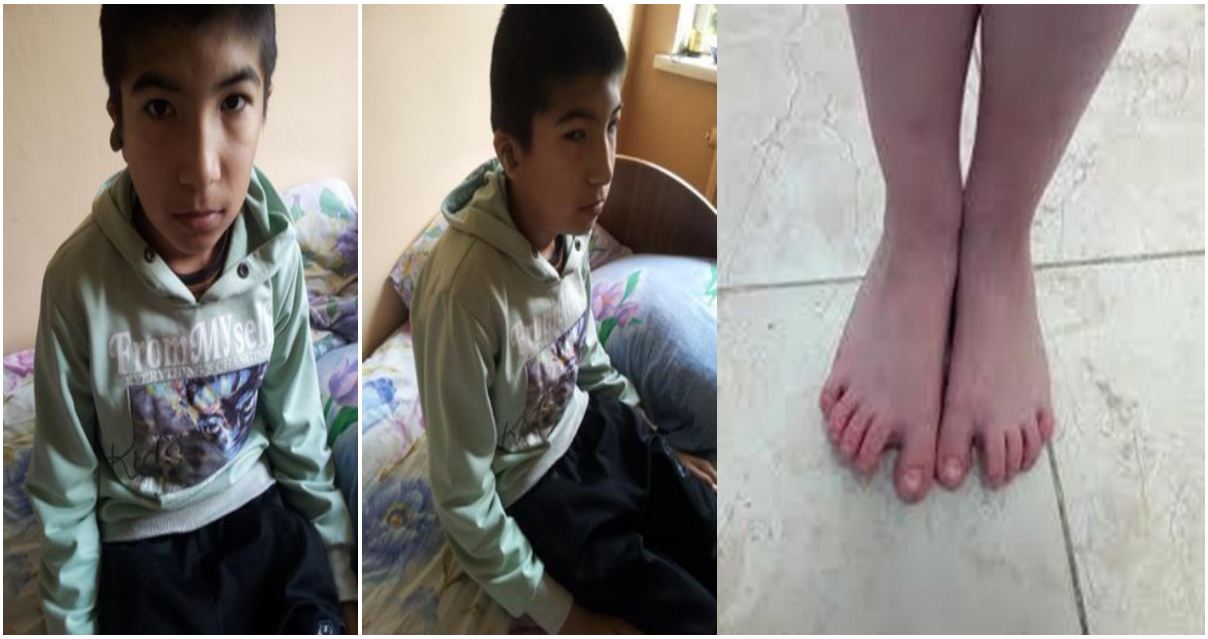

Fig.1, 2. Anomaly of the auricles, hair growth to the forehead, hypertelorism of the eyes, sandal-shaped gap between 1-2 toes.

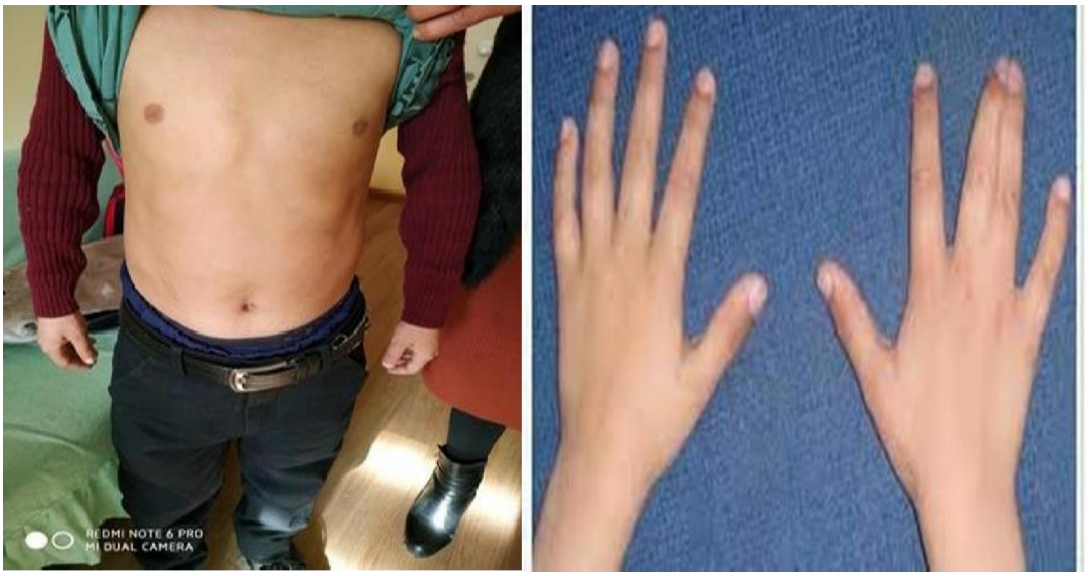

Fig .3, 4. Hypertelorism of the nipples, syndactyly of the right hand.

In our research (Table.1) the most distinctive stigmas of dysembriogenesis were epicanthus (P<0.05), chest deformity (P<0.001), hypertelorism of the eyes (P<0.001), pronounced brow ridges (P<0.01), anomaly of the auricles (P<0.05), hair growth to the forehead (P<0.01) sandal-shaped slit between 1-2 fingers of the hands and feet (P<0.01) (Table 2).

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Tab 1

The frequency of dysembriogenesis stigma in children with Alport syndrome (M±m)

№	Stigmas	Children with Alport syndrome (n =12)		The control group (n = 30)		P
		Абс.	%	Абс.	%	
5. Skull abnormalities						
1	Brachy- and dolichocephaly	1	8,3	-	-	-
2.	Flattened nape	2	16,7	2	6,6	< 0,01
3.	Pronounced brow ridges	2	16,7	1	3,3	< 0,01
II. Anomalies of the face						
1	Saddle-shaped, flattened nose	1	8,3	3	10,0	< 0,05
2.	Hypertelorism of the eyes	3	25,0	1	3,3	< 0,001
3.	Epicanthus	4	33,3	3	10,0	< 0,05
4.	High Gothic sky	2	16,7	1	3,3	< 0,05
5.	Anomaly of the auricles	2	16,7	4	13,3	< 0,05
6.	Dysplastic growth	1	8,3	5	16,7	< 0,05
7.	Hair growth to the forehead	1	8,3	-	-	-
III. Anomalies of the trunk, limbs						
1.	Sandal-shaped gap between 1-2 fingers of the hands and foot	2	16,7	1	3,3	< 0,01
2.	Nipple hypertelorism	3	15	2	6,6	< 0,001
3.	Chest deformity	4	33,3	1	3,3	< 0,001
4.	Clinodactyly	2	16,7	3	10,0	< 0,05
5.	Syndactyly	1	8,3	-	-	-

Conclusion:

1. Currently, orphan diseases in children (Alport syndrome) are underdiagnosed, and timely detection of the stigma of dysembriogenesis plays an important role in early diagnosis of the disease.
2. Stigmas of dysembriogenesis, such as a flattened occiput, pronounced brow ridges, hypertelorism of the eyes, epicanthus, high Gothic palate, anomaly of the auricles, hypertelorism of the nipples, chest deformity, sandal-shaped gap between 1-2 fingers of the hands and foot, clinodactyly can be considered as early phenotypic signs of Alport syndrome in children.

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