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CONGENITAL IMMUNODEFICIENCY DISORDERS IN THE PEDIATRIC PRACTICE

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Introduction. Congenital (primary) immunodeficiency disorders are genetic pathology that affects the immune system function. Primary immunodeficiency affects cell maturation or function at different levels during hematopoiesis [1, 2]. These conditions are most often represented by a breakdown in one gene, which leads to an inadequate immune response to infectious agents, autoimmune disorders, malignant lesions, and allergic diseases as a result [3]. Such clinical presentation in patients leads to recurrent, protracted or severe infections because of common infection or opportunistic pathogens, and clinical picture and course of these diseases depending on the specific immunological the defect [4, 5]. Despite the fact that the understanding of the mutual friendly work of innate and adaptive, humoral and cellular immunity is quite widely described in the literature, congenital immunodeficiencies are still classified for practical purposes as those that don’t have complete understanding of its pathological nature [4, 6].

Today, about 300 types of primary immunodeficiencies have been identified, in another sources you can see information about 430 types [1, 7]. This group includes combined B and T cell deficiency, prevalence of antibody deficiency, disorders of immunodeficiency with regulatory disturbance, disorders of congenital phagocytosis, deficiency of congenital immunity, auto-inflammatory disorders, complement system deficiencies and other well-defined immunodeficiency syndromes [8].

Around the world, over 6 million people (approximately 1 in 10,000 people) have congenital immunodeficiencies and 70-90% among of them remains undiagnosed (IV) that is why the real frequency of those diseases is much higher. Data on the average life expectancy of such patients in different regions vary [10].

As primary immunodeficiency disorders are a heterogeneous group of rare hereditary diseases caused by various monogenetic immune defects, therefore for successful timely diagnostics it is necessary to use genetic methods [11]. The genetic causes of a lot of primary immunodeficiencies were newly developed, which allows an accurate diagnosis, parental counseling and prenatal testing. Mutations in more 500 different genes that cause congenital immunodeficiencies have already been described.

Primary immunodeficiencies are most often associated with childhood because such disorders were commonly diagnosed and treated by pediatricians [11]. But nowadays, thanks to the development of medicine, such patients are increasingly reaching the 18 years old age and moving into adulthood. Although we have such a positive trend, primary immunodeficiencies are still more of a pediatric problem.

Material and methods. This dates are performed the clinical case the child with congenital immunodeficiency complement.

General and medical history. The child is from 6th pregnancy. Pregnancy was without toxicity, without risk of miscarriage. The gestational age of pregnancy at 39 weeks, physiological delivery was without complications. The child was born in full-term. The weight at birth was 3.49 kg, height – 52 cm. The gneiss was on the scalp, the skin was without rashes. Prolonged jaundice was not present. The child was attached to the breast immediately after birth.

The low weight was from 6 months. Also child held up the head from 3 months and rolled over at 4 months, set – at 7 month, started walking – at 11 month. First teeth were at 8 months. Late teething was in boy; by 1 year were 4 teeth. The patient started to talk with collocations at 2 years. The psychical and mental developments were according to the age periods of childhoods.

Breastfeeding was long time, from the first day of life. From 2 weeks child had pronounced intestinal colic. From 2 months diaper rashes were appeared on extensor surfaces, in the area of the ankle joints, neck. Treatment of diaper rashes were without effect. Diaper rash were with intensive redness and severe itching, despite that the child had breastfeeding and the mother had hypoallergenic diet. The one of complains was the intensive pain of the abdominal region after feeding.

Periodically, the child had diarrhea, stools in large volumes, with defecation 7-8 times per day. Also child has a food allergy, since 4 years he had allergic rhinitis, eczema of the hands.

At 6 years physical development had the decreased level: low at the weight (16 kg, less than 5 percentile), low height (110 cm, less than 30 percentile).

Atopic dermatitis, infant form was diagnosed by a dermatologist. Lactose intolerance, chronic gastritis, dolichosigma, biliary dyskinesia were observed by a gastroenterologist.

Also he usually has 2 times per year respiratory diseases, with bacterial complications, such as purulent otitis, obstructive bronchitis each times.

Parameters immunological blood test are presented: Immunoglobulin IgA – 1.09 g/l (reference value 0.27-1.95), Immunoglobulin IgM – 0.93 g/l (reference value 0.24-2.1), Immunoglobulin IgG – 9.8 g/l (reference value 5.04-14.64), Immunoglobulin IgE – 1796 kU/l, Circulating immune complexes – 53 ODU (reference value <115), Compliment activity – 65 LO (reference value 36-74), T-lymphocytes (CD3+) – 64.4% (reference value 59-78), T-lymphocytes (CD3+) – 1.21x10*9/l (reference value 1.4-3.8), cytolytic T-lymphocytes (CD3+CD16/56+) – 2.4% (reference value 0-10), % of activated T-lymphocytes (CD3+HLA-DR+) – 2.7% (1-8), T-helpers (CD3+ CD4+) – 44.3% (reference value 32-45), T-helpers (CD3+ CD4+) – 0.84x10*9/l (reference value 0.7-2.8), % of activated T-helpers (CD3+CD4+HLA-DR+) – 2.5% (reference value 1-8), T-cytotoxic lymphocytes (CD3+CD8+) – 16.8% (reference value 21-35), T-cytotoxic lymphocytes (CD3+CD8+) – 0.32x10*9/l (reference value 0.5-1.8), % of activated T-cytotoxic lymphocytes (CD3+CD8+HLA-DR+) – 4.1% (reference value 1-12), B-lymphocytes (CD19+) – 0.432x10*9/l (reference value 0.5-1.1), NK cells (CD3-CD16/56+) – 11.2% (reference value 6-20), NK cells (CD3-CD16/56+) – 0.209x10*9/l (reference value 0.1-0.9).

In immunological blood test was a detected decreased level of CD3+-lymphocytes, CD3+CD8+-cytotoxic lymphocytes, CD19 +-lymphocytes.

Gene panel of boy identifies one pathogenic variant in C8B (c. 1282C>T (p.Arg428*)), heterozygous, one heterozygous variant in C3 (c.2402C>T (p.Thr801Met)), which is associated with autosomal recessive and dominant. Uncertain Significance variants were detected, such as CBL c.1849C>T (p.Arg617Trp), heterozygous; DNAH11 c.12475G>T (p.Val4159Leu), heterozygous; IGLL1 c.221G>A (p.Arg74His), heterozygous; IL1RN c.535G>T (p.Asp179Tyr), heterozygous; POLE c.3890C>T (p.Ser1297Leu), heterozygous; PSMB8 c.730G>A (p.Gly244Ser), heterozygous; RIPK1 c.1276T>C (p.Tyr426His), heterozygous; STAT5B c.1975C>T (p.Arg659Cys), heterozygous; TONSL c.1114G>C (p.Val372Leu), heterozygous variants.

The result of genetic testing should be interpreted within the context of additional laboratory results, family history and clinical findings for appropriate next steps for further evaluation.

Clinical findings. Allergic skin symptoms (atopic dermatitis, eczema), persistent bacterial infections of the upper and lower respiratory tract, late teething, diarrhea, chronic diseases of the gastrointestinal tract are manifestations of immunodeficiency states.

Family history. A positive allergic family history was presented. Positive genetic tests of family history also were detected. In the father one pathogenic variant was identified in C8B. C8B is associated with autosomal recessive C8 beta deficiency. Gene panel of the father identifies one pathogenic variant in C8B (c.1282C>T (p.Arg428*)), heterozygous. Additional variant(s) of uncertain significance identified, such as IGLL1 c.221G>A (p.Arg74His), heterozygous; POLE c.3890C>T (p.Ser1297Leu), TONSL c.1114G>C (p.Val372Leu), heterozygous.

In the mother variants of uncertain significance were identified, such as C3 c.2402C>T (p.Thr801Met) heterozygous variant. RIPK1 c.1276T>C (p.Tyr426His), heterozygous. Uncertain significance variants were detected STAT5B c.1975C>T (p.Arg659Cys), heterozygous.

The sister of patient have the next uncertain significance variants, which were identified by genetic panel - RIPK1 c.1276T>C (p.Tyr426His), heterozygous; STAT5B c.1975C>T (p.Arg659Cys), heterozygous [12].

Conclusions. Genetic testing for identifying of congenital defects is very important. The testing was estimated, according the context of laboratory results, clinical symptoms and history of present illness. Analysis of genes has become indispensable for diagnostic process and appropriate next steps for prognosis.

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SUMMARY

CONGENITAL IMMUNODEFICIENCY DISORDERS IN THE PEDIATRIC PRACTICE

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Introduction. Congenital immunodeficiency disorders are genetic pathology that affect the immune system function and is important problem of modern medicine.

Material and methods. This dates are performed the clinical case of the child with congenital complement deficiency.

Results. Patient was diagnosed with allergic skin symptoms (atopic dermatitis, eczema), persistent bacterial infections of the upper and lower respiratory tract, late teething, diarrhea, chronic diseases of the gastrointestinal tract. That signs were manifestations of immunodeficiency states. During clinical and paraclinical examination the following data was detected in immunological blood test: decreased levels of CD3+-lymphocytes, CD3+CD8+-cytotoxic lymphocytes, CD19 +-lymphocytes. Gene panel of boy identifies one pathogenic variant in C8B (c. 1282C>T (p.Arg428*)), heterozygous, one pathogenic variant in C3 (c.2402C>T (p.Thr801Met)), heterozygous, which is associated with autosomal recessive and dominant. Uncertain significance variants were detected. Genetic signs in family members were also detected.

Conclusion. Genetic testing for identifying of congenital defects is very important in primary immunodeficiency diagnostic process.

Key words: children, primary immunodeficiency, complement deficiency.

РЕЗЮМЕ

ВРОДЖЕНІ ІМУНОДЕФІЦИТИ В ПЕДІАТРИЧНІЙ ПРАКТИЦІ

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Резюме. Вроджені імунодефіцити – це генетична патологія, що спричиняє дисфункцію імунної системи та є важливою проблемою сучасної медицини.

Матеріали і методи. Інформацію представлено у вигляді аналізу клінічного випадку дитини з вродженим дефектом системи комплементу.

Результати. У хворого діагностовано шкірний синдром алергічного ґенезу (атопічний дерматит, екзема), персистуючі бактеріальні інфекції верхніх і нижніх дихальних шляхів, пізнє прорізування зубів, діарея, хронічні захворювання шлунково-кишкового тракту, причиною розвитку яких є імунодефіцитний стан. Під час клініко-параклінічного обстеження в імунологічному дослідженні крові виявлено: зниження рівня CD3+-лімфоцитів, CD3+CD8+-цитотоксичних лімфоцитів, CD19+-лімфоцитів. Генетичне тестування показало наявність гетерозиготних патогенетичних мутацій у C8B (c. 1282C>T (p.Arg428*)), C3 (c.2402C>T (p.Thr801Met)), що асоціюються з аутосомно-рецесивним і домінантним типом наслідування. Ознаки генетичної патології також було встановлено у членів родини хворого.

Висновки. Генетичне тестування є дуже важливою складовою під час первинної діагностики вроджених імунодефіцитів.

Ключові слова: діти, вроджені імунодефіцитні стани, дефект системи комплементу.

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