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DIAGNOSIS AND MANAGEMENT OF THE IPEX SYNDROME

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Резюме. В данном исследовании представлен клинический случай синдрома IPEX у ребенка 5 лет. Клинические признаки, лабораторные исследования и осложнения анализировались с использованием медицинской карты указанного пациента.

Ключевые слова: IPEX синдром, дети.

Resume. In this study, a clinical case of the IPEX syndrome in a child aged 5 years is being presented. Clinical signs, laboratory analysis and complications were analysed by using medical cards of the said patient.

Keywords: IPEX syndrome, children.

Relevance. IPEX syndrome is an X-linked inborn error of immunity clinically characterized by the triad of: enteropathy, polyendocrinopathy and eczema. The occurrence of IPEX syndrome is below 1:1,000,000. IPEX syndrome is a condition that mainly affects males. The primary cause is a genetic mutation that results in an abnormal transcription factor called forkhead box P3 (FOXP3). Without this protein, T regulatory cells cannot develop properly, leading to a decrease in CD4+CD25+ T regulatory cells and uncontrolled proliferation of activated CD4+ effector cells. This ultimately leads to autoimmunity.

Enteropathy is present in almost all affected individuals. The enteropathy is marked by watery diarrhea, which can also contain mucus and blood, and can cause malabsorption, failure to thrive, and cachexia. Other gastrointestinal symptoms may include colitis and gastritis, as well as food allergies.

Endocrinopathy is another common manifestation of IPEX syndrome, with type 1 diabetes mellitus being the most frequent endocrine disorder. Thyroid disease is also often present.

Dermatitis is a common symptom of IPEX syndrome, most frequently appearing as eczematous dermatitis, but psoriasiform and ichthyosiform dermatitis have also been reported

Individuals with IPEX syndrome also often develop autoimmune disorders, with cytopenias, autoimmune hepatitis, and nephropathy (including membranous nephropathy, interstitial nephritis, and rarely minimal change nephrotic syndrome) being among the most common. Lymphadenopathy and splenomegaly resulting from lymphoproliferation have also been observed.

Infectious complications are another frequent occurrence in individuals with IPEX syndrome, with gastrointestinal, skin, and airway infections being particularly common. A

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significant number of individuals also experience severe or invasive infections, such as sepsis, meningitis, pneumonia, and osteomyelitis.

Aim: to present a clinical case of the IPEX syndrome in a child aged 5 years.

Materials and methods. Analysis of over 100 articles sourced from PubMed, Google Scholar and UpToDate databases and the presentation of the clinical cases of the 5-year-old male patient.

Results and their discussion. The child was born on June 6, 2014, from the 2nd pregnancy and 2nd delivery. Delivery occurred at 39 weeks of gestation with a threatened miscarriage at 32 weeks. Birth weight was 3400g, length was 52cm. The child was artificially fed during the first year of life and developed atopic dermatitis from the first year of life, along with multiple episodes of obstructive bronchitis. The child received age-appropriate vaccinations until the age of 2 and development was normal for their age. There is no family history of illness.

In 2016, the child was hospitalized due to a localized herpes infection of the oral mucosa, including stomatitis and glossitis. This was the first time that changes in urinalysis were detected (protein 1.2g/L, erythrocytes up to 10-15 in p/f, and leukocytes in large amounts). In addition, laboratory testing revealed hypoproteinemia, hypoalbuminemia, and hypercholesterolemia. Upon discharge, the urinalysis had normalized, which was interpreted as an infectious-toxic kidney.

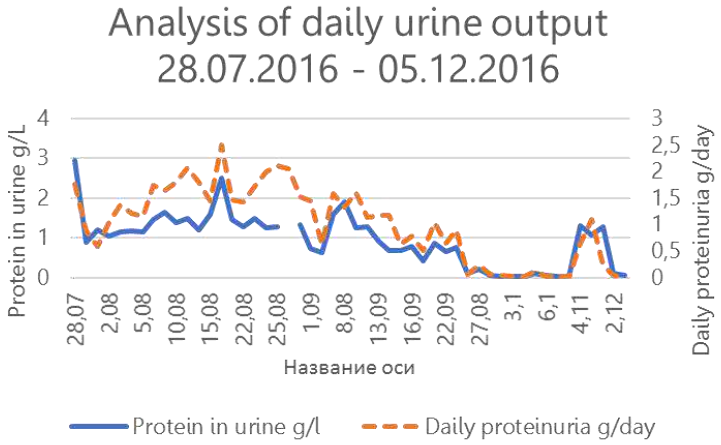

Fig.1 – Analysis of daily urine output 28.06.2016 – 05.12.2016 (L)

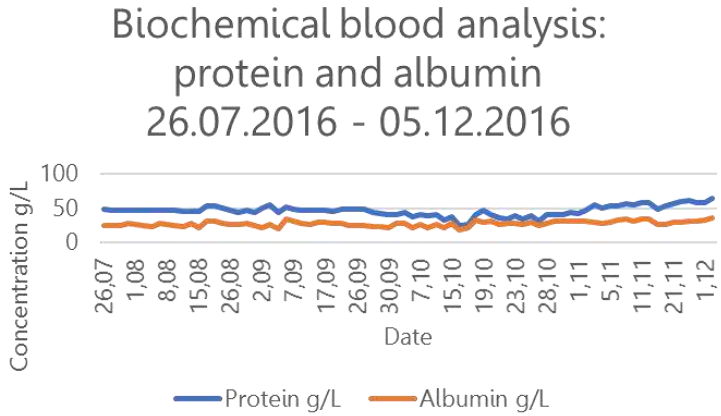

Fig. 2 – Biochemical blood analysis 28.06.2016 – 05.12.2016 (R)

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A month later, there were further changes in laboratory tests, with proteinuria, micro- and macrohematuria, hypoalbuminemia, and hypercholesterolemia detected in urinalysis and blood tests. The child was urgently admitted to the nephrological department for examination and treatment. The diagnosis was incomplete nephrotic syndrome with hematuria during a period of active symptoms. The child was prescribed corticosteroid therapy with an initial dose of 2mg/kg/day of prednisolone. However, after 7 weeks of treatment with this dose, the child's laboratory signs of nephrotic syndrome persisted (hypoproteinemia, hypoalbuminemia, hypercholesterolemia, and daily proteinuria greater than 50mg/kg), requiring periodic transfusions of 20% albumin. Therefore, the child underwent pulse therapy with methylprednisolone at a dose of 20mg/kg for three consecutive days. Although there was a positive trend in the urinary syndrome, hypoproteinemia and hypoalbuminemia persisted, but did not require albumin transfusion. The child was then switched to alternating doses of prednisolone at 2mg/kg/48 hours, with a gradual reduction in dosage.

Three months after the start of treatment, the patient's condition worsened, with the addition of gastrointestinal symptoms such as bloating, increased abdominal volume, frequent bowel movements (10-17 times per day), and weight loss. Esophagogastroduodenoscopy with biopsy of the duodenal papilla was performed and showed morphologically verified atrophic duodenitis. Screening for celiac disease revealed elevated IgG and IgA antibodies to gliadin. The patient was started on a gluten-free and dairy-free diet, and the condition was diagnosed as autoimmune enteropathy.

Immunological examination did not reveal primary immunodeficiency, including chronic granulomatous disease.

After strict diet therapy and corticosteroid therapy for 3-4 months, gastrointestinal symptoms improved, the patient began to gain weight, and the level of antibodies to gliadin decreased. The patient was diagnosed with celiac disease and was followed by a pediatrician and specialists from 2017-2019 with a diagnosis of nephrotic syndrome, recurrent course, celiac disease, atopic dermatitis, and multiple allergies.

During a worsening of clinical status and laboratory parameters of nephrotic syndrome, the patient received corticosteroid therapy and maintained a strict gluten-free diet.

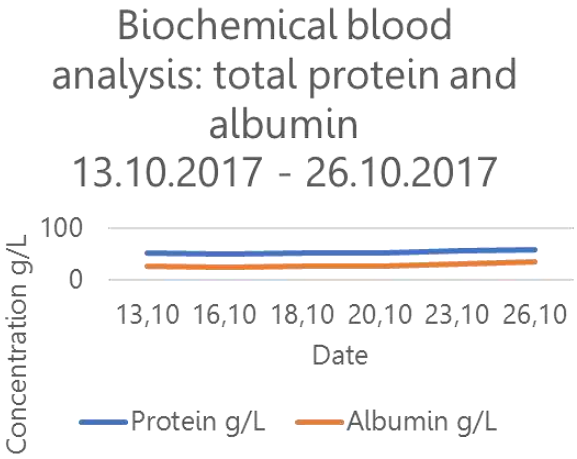

Fig. 3 – Biochemical blood analysis: total protein and albumin 16.10.2017 – 26.10.2017 (Above)

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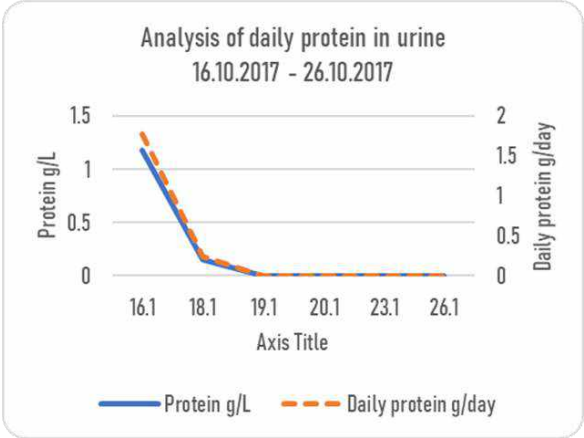

Fig. 4 – Analysis of daily protein in urine 16.10.2017 – 26.10.2017 (Below)

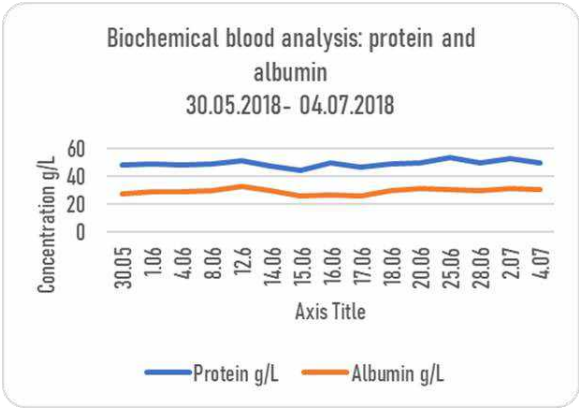

Fig. 5 – Biochemical blood analysis 30.05.2018 – 04.07.2018

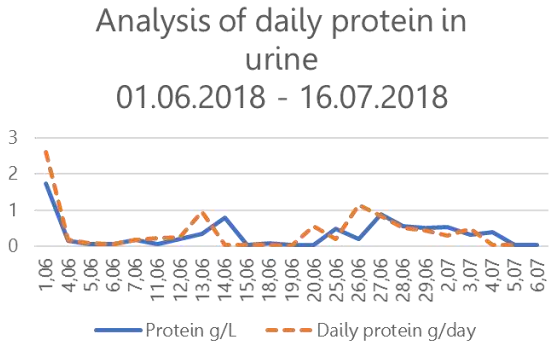

Fig. 6 – Analysis of daily protein in urine 01.06.2018 – 16.07.2018

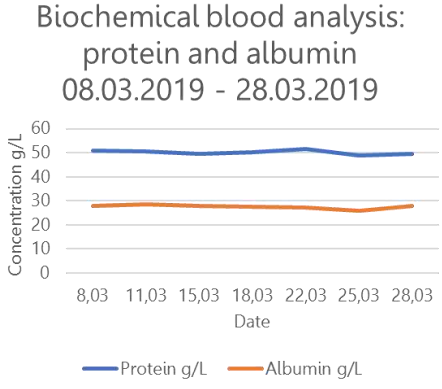

Fig. 7 – Biochemical blood analysis 08.03.2019 – 28.03.2019

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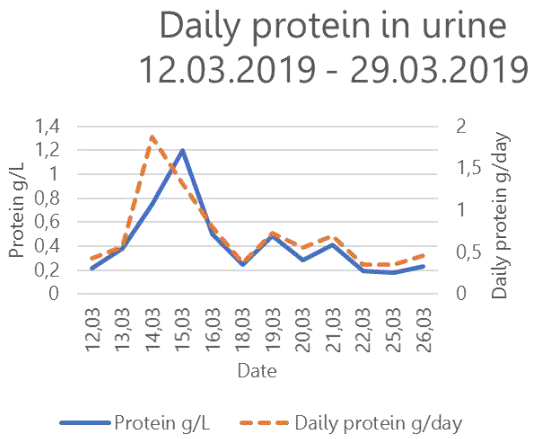

Fig. 8 – Daily protein in urine 12.03.2019 – 29.03.2019

In February 2020, a kidney biopsy revealed signs of membranous nephropathy. From March 2020, the patient's condition deteriorated, with loose stool, signs of hypoproteinemia and hypoalbuminemia, hypogammaglobulinemia, edema, and decreased electrolyte levels without significant changes in urine analysis. Esophagogastroduodenoscopy revealed total atrophy of the mucosa of the duodenum, superficial gastritis, and cardia insufficiency. Colonoscopy revealed hypotrophy of the mucosa of the distal parts of the small intestine, dilatation of the lumen of the colon, and signs of acute unexpressed colitis. Due to the combination of symptoms (nephropathy, enteropathy, dermatitis, resistance to therapy), genetic testing was performed to exclude primary immunodeficiency.

The results of genetic testing showed a positive result of the pathogenic variant of FOXP3 (variant c.748_750del (p.Lys250del)), and the patient was diagnosed with IPEX syndrome. The patient was transferred to a specialized center for further treatment and has been receiving sirolimus with monitoring of blood levels and maintaining a gluten-free diet since June 2020.

Conclusion In recent years, although IPEX syndrome is characterized by inflammatory bowel disease, type I diabetes, and skin diseases, the number of IPEX cases exhibiting atypical symptoms was increasing. In our case, the patient except atopic dermatitis suffered from proteinuria, chronic gastritis and bronchial asthma. These symptoms were not the primary symptoms of IPEX syndrome. Therefore, through this case, we recognize that the consideration of IPEX syndrome is important when a child develops multiple system disorders.

References

1. Park J. H. et al. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome: a systematic review //Autoimmunity Reviews. – 2020. – Т. 19. – №. 6. – С. 102526.

2. Tan Q. K. G., Louie R. J., Sleasman J. W. IPEX syndrome. – 2018.

3. Ben-Skowronek I. IPEX syndrome: genetics and treatment options //Genes. – 2021. – Т. 12. – №. 3. – С. 323.

4. Barzaghi F., Passerini L. IPEX syndrome: improved knowledge of immune pathogenesis empowers diagnosis //Frontiers in pediatrics. – 2021. – Т. 9. – С. 612760.

5. Mendonça L. O. et al. Underlying IPEX syndrome in a patient with idiopathic juvenile arthritis and vitiligo //Allergy, Asthma & Clinical Immunology. – 2022. – Т. 18. – №. 1. – С. 1-6.