Cryopyrin-associated periodic syndrome Muckle — Wells: A Case Report

SCO — краткое сообщение

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Криопирин-ассоциированный периодический синдром Макла — Уэллса: клинический случай

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Relevance. Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory diseases that includes familial cold autoinflammatory syndrome (FCAS), Muckle — Wells syndrome (MWS) and chronic infantile neurological, cutaneous and articular syndrome (CINCA), also known as neonatal onset multisystem inflammatory disease (NOMID) [1, 2]. These syndromes were initially described as separate nosological forms, despite some clinical similarities: patients often experience cross symptoms, including лихорадку, skin rash, resembling hives, and joint damage of various severity, associated with systematic inflammation [3, 4, 5]. These three diseases constitute a continuum in severity: FCAS is a mild disease, CINCA/NOMID is most severe, and patients with MWS have an intermediate phenotype. The basis of the CAPS pathogenesis is NLRP3 gene mutation, encoding cryopyrin protein that leads to uncontrolled inflammasome activation and increase in interleukin-1 (IL1) expression [6]. Rash and fever are the first and very frequent CAPS symptoms and patients are often observed in doctors of different profiles with incorrect diagnosis for a long time. Despite the fact that CAPS is referred to extremely rare diseases, most doctors' insufficient knowledge in autoinflammatory syndromes allows to speak about underdiagnosis of these conditions. We present a clinical case of Muckle — Wells syndrome in a 4-year-old child.

The mother of the 4-year-old child consulted a doctor-allergist immunologist complaining about the child's rash, localized on the trunk, limbs, not accompanied by itching, not disappearing with intake of antihistamines, and progressive pain in the joints of the lower extremity.

It is known from the history of the disease that rash appeared from the first days of the child's life. The boy was repeatedly consulted by dermatologists and allergists-immunologists, who examined him with diagnoses: atopic dermatitis, chronic urticaria. He repeatedly re ceived local anti-inflammatory therapy with glucocorticosteroids and calcineurin inhibitors, systemic antihistamines with no effect. In addition to rash, the child experienced persistent leukocytosis within 20–23 K/mcL, periodic increase in ESR up to 20–30 mm/h without clinical and laboratory signs of infectious process, and iron deficiency anemia from the first months of life. Periodic pain in the joints of the lower extremity appeared at the age of 3 years. Complete blood count in the first three years of life:

1 year — hemoglobin 108 g/l, leukocytes 20 K/mcL, ESR 17 mm/h; 2 years — hemoglobin 107 g/l, leukocytes 23 K/mcL, ESR 23 mm/h; 3 years — hemoglobin 114 g/l, leukocytes 19 K/mcL, ESR 19 mm/h, 4 years — hemoglobin 107 g/l, leukocytes 23 K/mcL, ESR 23 mm/h.

Objective status when consulting a doctor allergist-immunologist. Physical development is average, harmonious. Neuropsychological development is age-appropriate. The child's well-being is not impaired. There is maculopapular urticarial-like rash on the face, trunk, upper and lower extremities. From the internal organs — without pathology. Laboratory examination identifies leukocytosis 21 K/mcl, ESR 30 mm/h, CRP 17 mg/l. There are no signs of an infectious process at the time of examination. To clarify the diagnosis the child is hospitalized to the immunology department of FSBI "Dmitriy Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology". The data of laboratory and instrumental studies: hemoglobin 114 g/l, leukocytes 21,8 K/mcL, platelets 455 K/mcl, ESR 77 mm/h, CRP 17 mg/l. Immunophenotyping lymphocytes — no significant deficiency in the major subpopulations of lymphocytes: CD3+ 6,23 K./mcl, $CD4^+$ 3,96 K./mcl, $CD8^+$ 1,86 K./mcl, $CD19^+$ 1,66 K./mcl. Immunoglobulins of blood serum are within reference values. Antinuclear screening (anti-dsDNA, ANA, antiphospholipid syndrome) — autoantibodies are not found. Ultrasound of the abdominal organs — signs of intra-abdominal lymphadenopathy, diffuse parenchymal changes of the pancreas. When examining fundus of the eye with the slit lamp — signs of optic disc nerve inflammation. Lumbar puncture — cytosis 21,5/mm^3. MRI of the brain with intravenous contrast — without pathology. Molecular genetic study: next generation sequencing (NGS, NMRC PHOI laboratory, immunological panel), mutation in the gene NLRP3 c.9l3G>A, p.Asp305Asn in the heterozygous state. Based on anamnesis data — urticarial-like rash from the first days of life, arthralgia episodes, physical examination findings — a wide spread maculopapular, urticarial-like rash, laboratory and instrumental examination methods — leukocytosis, an increase in ESR and CRP with no signs of the infectious process, optic disc nerve inflammation, increased cytosis in the cerebrospinal fluid, and also the results of molecular genetic studies — pathogenic mutation in NLRP3 gene; the diagnosis was made: primary immunodeficiency state: autoinflammatory syndrome — cryopyrin-associated periodic syndrome (Muckle-Wells syndrome) (mutation in the gene NLRP3 c.913G>A, p.Asp305Asn in the heterozygous state). *Complication*: optic nerve disk congestion; optic neuritis.

The patient was initiated pathogenetic therapy with monoclonal antibody to interleukin 1β — canakinumab at a dose of 5 mg/kg once every 8 weeks. The positive dynamics was noted after the first administration of the drug — complete rash resolution, leukocytes decreased to 15,8 K/mcl, ESR 25 mm/h, CRP 7,5 mg/l. laboratory indicators after the 4^{th} administration of canakinumab — leukocytes 9,8 K/mcl, ESR 7 mm/h, CRP — отр.

Conclusion. In the presented case the rash on the child's skin, appeared from the first days of life, was considered as skin disease — chronic urticarial and atopic dermatitis, despite the lack of effect from antihistamine and topical anti-inflammatory drugs. Arthralgia, signs of inflammation in the form of persistent leukocytosis, ESR acceleration with the absence of foci of infection were not taken into account for a long time that led to delay in diagnosis, the lack of adequate therapy and the development of complications as facial palsy.

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