PERIODIC SYNDROME ASSOCIATED WITH THE MUTATION OF THE RECEPTOR GENE OF THE TUMOR NECROSIS FACTOR (CLINICAL CASE)

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ABSTRACT

The paper deals with a case of TRAPS in a Ukrainian family. The manifestations of this syndrome appeared at the age of 2.5 years and gradually the attacks of fever became more frequent and the recurrence was typical of this diagnosis. Classically, besides fever, there was an intense abdominal pain, such as an “acute abdomen”, arthralgia in the right hip and headache. Micropolialdenia was also detected. This patient did not have any other symptoms. A genetic study found a mutation in the TNFRSF1A gene (substitution in exon 4 with 3449T>G: p.C117G). This mutation has not been recorded in the international electronic database INFEVERS. The child was administered pathogenetic therapy with a selective blocker of interleukin (IL-1) receptors (anakinra) at a dose of 1-5 mg / kg of body weight subcutaneously daily. After the first injection of anakinra the patient got rid of fever, joint syndrome and of abdominal pain. After 1 week of therapy, laboratory parameters of the disease activity (ESR, CRP) became normal. The child has taken anakinra for two years, there were no exacerbations of the disease or side effects due to the treatment.

The variety of clinical manifestations of congenital periodic fever and the presence of previously unknown genetic mutations that lead to the development of auto-inflammatory syndromes, indicate the need for a detailed study of these diseases.

KEY WORDS: Autoinflammatory diseases, TRAPS syndrome, child, fever, anakinra

INTRODUCTION

In recent decades, more and more of specialists' attention has been attracted to the diseases which belong to a group of autoinflammatory diseases or syndromes (AIS). According to modern views, the term human autoinflammatory diseases (HAIDS) is understood as a heterogeneous group of rare, genetically determined conditions characterized by periods of inflammation of non-infectious genesis. These diseases manifest themselves with recurrent fever and symptoms that resemble rheumatic or autoimmune diseases, in the absence of autoimmune or infectious causes [1].

In everyday clinical practice, these diseases are quite varied in their manifestations, so there are some difficulties in their diagnosis. In the clinical picture of AIS there are recurrent episodes of the systemic inflammatory process, which manifest with aseptic inflammation of serous and mucous membranes, joints, tonsils, and skin [2,3]. This symptomatology, combined with elevated ESR, rates of leukocytes, fibrinogens, serum amyloid A (C AA), and a low risk of developing amyloidosis, is typical of this group of diseases. This clinical picture also occurs in rheumatologic practice, therefore patients are often initially referred to a rheumatologist.

Autoinflammatory diseases are known in the literature as syndromes of periodic fever and caused by a defect in regulation of innate immune response with inappropriate activation of interleukin-1 and tumor necrosis factor [4]. These diseases are different from classical autoimmune disorders as they are not mediated by autoantibodies. Patients do not have high titres of autoantibodies or antigen-specific T-cells that are commonly seen in autoimmune diseases [5,6]. They most often appear in childhood, sometimes in the first year of life, and therefore, it is a pediatric problem first of all. Most of the diseases in this group belong to a rare pathology. These are monogenic diseases caused by the mutation of one gene, inherited by the autosomal recessive or autosomal dominant type [3].

According to the EUROFEVER registry, obtained from 37 countries of the world (data provided on the PRINTO website), more than 3,000 patients with auto-inflammatory syndromes have been recorded.

The list of AIS is presented in various classifications and according to the EUROFEVER project, is quite voluminous [7,8]. It includes various groups of diseases and syndromes, including those that are encountered in their practice by pediatric rheumatologists and, to a lesser extent, adult rheumatologists.
They include a number of monogenic periodic fevers, namely, Familial Mediterranean fever (FMF), Cryopyrin-associated periodic syndrome (CAPS) that include Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), NOMID/CINCA syndrome, hyper-IgD/HIDS/ mevalonate kinase deficiency syndrome (MKDS), TRAPS syndrome – a periodic syndrome associated with a mutation of the tumor necrosis factor receptor gene α and other conditions related to multifactorial diseases: Behcet’s disease (BD), PFAPA (Marshall Syndrome), etc. The list of AIS is steadily rising, revealing new genetic mutations, characteristic of one or another AIS [9].

The «classic» example of AIS is a periodic syndrome associated with the mutation of the tumor necrosis factor receptor gene (TNF) – TRAPS (TNF-receptor-associated periodic syndrome), which was first described in 1982 by an example of members of a large Irish family [10]. Fietta P. points out that it was an example of TRAPS that was used by a prominent American researcher Kastner D.L. and his co-authors to first formulate the concept of auto-inflammation [1].

TRAPS is a monogenic disease (MIM #142680) that is caused by a mutation of the TNFRSF1A gene, mapped on the short arm of the chromosome 12 (12p13) [11]. The disease is inherited by the auto-dominant type. The TNFRSF1A gene encodes a type I receptor with a molecular weight of 55 kDa for tumor necrosis factor α (TNFα) (the most important proinflammatory cytokine produced mainly by monocytes/macrophages, lymphocytes, NK cells, polymorphonuclear leukocytes) [3,5,6]. The effects of TNFα are carried out by binding to receptors of type I with a mass of 55 kDa and type II with a mass of 75 kDa. As a result of interaction with the receptors, a series of intracellular signaling processes is triggered, which results in or activation of the factor NFκB (a universal transcription factor that controls the expression of the genes of the immune response, apoptosis and the cell cycle) and the expression of the genes of the inflammatory mediators (proinflammatory cytokines) or to the induction of apoptosis [3,6,12].

To date, more than 70 TNFRSF1A gene mutations associated with the development of TRAPS have been known. All mutations are located in those parts of the gene that encode the extracellular part of the receptor molecule. The vast majority of mutations are located in Exons 2, 3, 4, encoding the first two N-terminally located cysteine-enriched domains (CRD1 and CRD2) of the TNF receptor molecule 55. CRD1 is a preligand binding domain, which provides for the self-assembly of the receptor molecule by interaction with a ligand that enables effective reception and signaling. CRD2 directly binds to the TNFα molecule. 94% of known mutations are missense mutations that result in the replacement of amino acids in the structure of the protein molecule [12]. At TRAPS there is a pronounced genotype-phenotype correlation [12,13].

Such hypotheses are leading in the pathogenesis. The first one: mutations lead to a defect of the metalloproteinase-dependent cleavage of the receptor molecule, and as a result, it is peeled off from the cell surface, resulting in a decrease in the content of the soluble TNF receptor (pTNF55), which is a natural antagonist of the molecule of the ligand, in biological fluids, primarily in serum of the blood. Such a mechanism is characteristic of the mutations C33Y, T50M, C52F [12,13].

The second theory of pathogenesis, which is currently the most popular, involves a decrease in the TNFα-induced apoptosis of neutrophils and fibroblasts, which is characteristic of mutations that affect the cysteine residues of the receptor molecule, as well as impaired movement of the receptor molecule I (pTNF55) from the cytoplasm to the cell surface. Only a small portion of pTNF55 is expressed on the cell surface, and the large part of them is accumulated intracellular in the Golgi apparatus. After binding pTNF55 with the ligand on the cell surface, three pTNF5 molecules form a trimer, which leads to activation of the cell death domain.

Normal pTNF5 molecules are not capable of forming molecular aggregates within these cellular organelles, while mutant molecules, as a result of disorders in the formation of the polypeptide chain, are capable of forming aggregates that, in turn, lead to the formation of an activation signal without binding to the ligand, with a molecule of TNF. This activation signal leads to the induction of IL 1β. This hypothesis clearly explains the expressed therapeutic effect of anti-IL1 therapy in patients with TRAPS [12,14].

In this case, the mutant molecule of the receptor to the type I TNF (pTNF5) is accumulated in the endoplasmic reticulum and is perceived as an internal factor of damage and, being a pro-inflammatory stimulus, leads to a decrease in the threshold of sensitivity to external stimuli of natural immunity, resulting in hyperproduction of other pro-inflammatory cytokines, and also a disorder of the function of mitochondria with increased production of active forms of oxygen [15,16].

Initially, cases of TRAPS were described among Irish and Scottish people. However, currently, carriers of pathological mutations in the TNFRSF1A gene, suffering from TRAPS have been detected in various ethnic groups, including African Americans, Puerto Ricans, French, Belgians, Danes, Portuguese, Italians, Arabs, Jews, Germans, Finns [17], and Japanese [18].

On average, the disease begins at the age of 3 years, but can debut at the age from 2 weeks to 53 years. The duration of this attack is 5-6 weeks, although the reported cases of attack duration are 2-3 days, the average interval between attacks is 1 day, but it can vary widely.

The clinic of TRAPS is also characterized by: fever (100%), high intensity myalgia (almost 100% of patients), painful rash (erythema and swollen plaques) on the trunk and extremities with a tendency toward distal migration (> 60%), intense abdominal pain, such as «acute abdomen», which may be accompanied by constipation or diarrhea, nausea, vomiting. Also for the TRAPS clinic is characteristic by: painful conjunctivitis with periorbital edema, sometimes uveitis; chest pain (50%), aseptic pleurisy; arthralgia in large joints, rarely – arthritis (asymmetric mono /
CLINICAL CASE

We would like to share our observation of TRAPS case in a Ukrainian family.

The patient O.I, born in 2012, was given birth after the fifth normal pregnancy, the childbirth was natural. The first two pregnancies ended in miscarriages in the early stages, two subsequent pregnancies ended with the birth of healthy children. The mother suffers from chronic pyelonephritis, the episodes being moderate, accompanied by abdominal pain, absence of hemato-oncological diseases, nonspecific autoinflammatory disease was suspected. The genetic examination was conducted in Moscow. The laboratory findings are characterized by an increase in acute phase indicators – ESR, C-reactive protein (CRP), haptoglobin, fibrinogen and ferritin, which can be kept elevated and outside the attack. Leukocytosis with neutrophilia, thrombocytosis, decreased hemoglobin levels are common. There is an increase in the level of immunoglobulins, in particular IgA; some patients have an IgD level (> 100 IU / ml). A typical laboratory finding in patients with TRAPS is a decrease in the levels of pptTNF55 below 1 pg / ml. However, the level of these receptors in the blood can sometimes reach normal values in the period of attack [5,17].

Based on the facts of attacks of periodic fever lasting 3-7 days every 3-5 weeks, the temperature gradually increased from subfebrile figures in the first 3 days to febrile ones (39-39.5°C) in the future, sometimes there was intense but short-term abdominal pain. The examination did not find any changes in the internal organs. The fever and abdominal pain were well eliminated by non-steroidal anti-inflammatory drugs (ibuprofen), but the period of lowering the temperature under the influence of the drug was unstable.

The episodes were accompanied by a significant increase in the level of acute phase markers of inflammation: leukocytes – 7-8\times10^9/l, ESR to 66 mm/h; anemia (Hb 90 g/l). The biochemical study found elevated levels of C-reactive protein> 48.0 mg/L (norm 0-6.0 mg/l).

The ultrasound of the cervical showed: on the right in the submandibular cervical region, normal sizes and structures of the lymph nodes with a maximum size of 15x9 mm are visualized. To the left of the angle of the mandible there are two lymph nodes with a usual structure size 19x8 mm and 15x7 mm. At the nodding muscle there were lymph nodes sized up to 10 mm. Anterior cervical lymph nodes were with a maximum size of 8 mm.

An ultrasound examination of the internal organs revealed an increase in the liver and spleen. The liver – the lower edge of the right lobe projects 30 mm, and the left one – 83 mm from the costal margin, the echogenicity of the parenchyma is normal, its texture is fine and homogeneous, the stroma of the liver is not condensed, not thickened. The spleen is slightly enlarged, structurally unaltered, with dimensions 98x27 mm, the lower edge protrudes 15 mm from the costal margin. At the lower pole of the spleen an additional lobe measuring 11 mm is visualized. The kidneys are not changed.

An ECG showed sinus arrhythmia with a heart rate of 81 per minute. The raised voltage of the QRST complex (preferably in the chest). The electric axis of the heart is vertical. Signs of increase of vagus influence and increase of electrical activity of the left ventricle are revealed. Echo-cardiography did not find any pathology.

When examined by specialists: the hematologist detected reactive cervico-submandibular lymphadenopathy and iron deficiency anemia, the surgeon did not detect any severe surgical pathology at the time of the examination.

The patient was recommended a genetic testing of a typical mutation in the \textit{TNFRSF1A} gene to exclude TRAPS syndrome.

The genetic examination was conducted in Moscow where a mutation in the \textit{TNFRSF1A} gene was detected (substitution in exon 4 with p.349T> G;p.C117G). This mutation is not recorded in the international electronic database INFEVERS, which contains information on mutation of genes associated with the development of AIS [19].

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Based on the facts of attacks of periodic fever lasting 3-7 days every 3-5 weeks, accompanied by abdominal pain, absence of hemato-oncological diseases, nonspecific ulcerative colitis, systemic rheumatologic diseases, as well as absence of Mediterranean fever (negative genetic tests), of hyperimmunoglobulin-D- syndrome, as well as on the...
results of the genetic study of the TNFRSF1A gene TRAPS syndrome was diagnosed.

The child was administered pathogenic therapy with a selective blocker of the interleukin (IL-1) receptor (anakinra) at a dose of 1-5 mg/kg of body weight subcutaneously daily.

After the first injection of anakinra fever, joint syndrome and abdominal pain disappeared. After 1 week of therapy, laboratory parameters of the disease activity (ESR, CRP) were normalized. The child has been taking anakinra for two years, the exacerbations of the disease were not noted, there were no unwanted phenomena due to the treatment.

DISCUSSION
The spectrum of autoinflammatory disorders has been constantly increasing with each passing year [20,21]. A detailed history collection provides invaluable information for a doctor who can differentiate between auto-inflammatory disorders, immunodeficiency or infection in childhood, accelerating diagnosis and avoiding unnecessary diagnostic studies [4,12].

The manifestations of this syndrome appeared at the age of 2.5 years and gradually the attacks of fever became more frequent and the recurrence was typical of this diagnosis. Classically, besides fever, there was an intense abdominal pain, such as “acute abdomen”, arthralgia in the right hip and headache. Micropoliodenia was also detected. This patient did not have any other symptoms. The syndrome was confirmed in the sixth year of the child’s life.

In recent years, using genetically engineered biological drugs has become a fundamentally new approach to TRAPS treatment [22]. The first of this class were TNFα inhibitors (infliximab, adalimumab), monoclonal antibodies to TNFα, which not only demonstrated low efficacy, but even provoked exacerbation of the syndrome [23]. The etanercept, a recombinant receptor-mediated drug, was more successful: a large number of patients achieved a state of improvement or remission, however, on average, after 3 years of treatment, they developed secondary ineffectiveness [24]. Most of these patients were transferred to IL-1 interleukin inhibitor, which showed the best effect in patients with TRAPS [25].

Autoinflammatory diseases can be considered as a natural experiment that reveals the clinical and pathological effects of unregulated IL-1-mediated inflammation in humans. Regardless of the main mechanisms, the manifestations of the disease are controlled by the blockade of IL-1 with the drug “anakinra”; as different pharmacokinetics result in longer duration of action, neutralizing antibodies directed against IL-1β (canakinumab) are an alternative in patients with frequent exacerbations of the disease.

Since its introduction in 2002, it has been estimated that more than 150,000 patients have taken anakinra, some of them took it daily for more than 10 years. Opportunistic infections in patients taking anakinra were rare [26], including the populations at high risk of M. tuberculosis [27,28].

CONCLUSIONS
1. The variety of clinical manifestations of congenital periodic fever and the presence of previously unknown genetic mutations that lead to the development of auto-inflammatory syndromes, indicates the need for a detailed study of these diseases.
2. This observation indicates the presence of a case of TRAPS syndrome in the Ukrainian population, with a non-typical mutation of the TNFRSF1A gene, which helped to administer pathogenic treatment with monoclonal antibodies to IL-1.

ABBREVIATIONS
AIS – autoinflammatory syndromes; ESR – erythrocyte sedimentation rate; TRAPS – tumor receptor associated periodic syndrome; TNFα – tumor necrosis factor α; CRP – C-reactive protein.

REFERENCES


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Conflicts of interest:
Authors declare no conflict of interest.

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Received: 10.05.2019
Accepted: 30.12.2019

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article