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# NLRP12-Associated Periodic Syndrome: An Analysis of Literature Data

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## ABSTRACT

Auto inflammatory diseases (AIDs) are a group of rare disorders characterized by persistent or recurrent inflammation caused by the hyper activation of mediators and innate immune cells (neutrophils, monocytes/macrophages). The paper describes the author reviews a series of cases of the similar disease, which are given in the literature.

**Keywords:** Auto inflammation, NLRP12, Inflammasome

## INTRODUCTION

Auto inflammatory diseases (AIDs) - a group of rare diseases characterized by persistent or recurrent inflammation, caused by the hyper activation of mediators and cells of congenital immunity (neutrophils, monocytes/macrophages). In contrast to autoimmune diseases in AVS, the involvement of T and B lymphocytes is only possible again, so there is no formation of autoantibodies and a connection with antigens of the main histocompatibility complex of HLA class II [1,2].

Innate immunity plays a crucial role in nonspecific protection of the body against infections using the system of recognizable receptors (pattern recognition receptors, PRRs). These receptors recognize the molecular sequences of pathogens and activate the immune response [3].

Interleukin 1 (IL1) is a key pro-inflammatory cytokine synthesized by monocytes, tissue macrophages and dendritic cells. Its formation is stimulated by the influence of microbial wall peptides, cytokines such as tumor necrosis factor (TNF), IL18, IL1 and IL1 itself [4]. Auto induction of IL1 synthesis is the main pathogenetic link of auto inflammation. IL1 is synthesized in an inactive form in the form of a precursor molecule of interleukin 1 (pro-IL1), which is activated by the enzyme caspase 1 (convertase IL1). Uncontrolled activation of the enzyme caspase 1 in patients with a mutation in the NLRP3 gene leads to the formation of a large amount of active IL1, which stimulates its own excess production.

This mechanism underlies cryopirin-associated periodic syndromes (CAPS), characterized by sterile multi-organ inflammation [5]. **In AIDS**, in contrast to autoimmune diseases, the use of IL1 blockers is effective, while blocking other cytokines does not produce a result [6].

CAPS is a group of hereditary diseases, represented by phenotypes, differing from each other in clinical manifestations and severity [7]. There are three forms of CAPS: Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and the neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as chronic Infantile skin neurological and articular syndrome (Chronic Infantile Neurological Cutaneous Articular Syndrome, CINCA) [8]. All three diseases are associated with the presence of activating mutations in the gene NLRP3 (CIAS1), which encodes the cryopirin protein (a key component of the inflammosome activatingcaspase 1) and determines the production rate of IL1 [9-11].

All three forms of the disease are characterized by episodes of fever, accompanied by the appearance of urticaroid-like rash, joint pain and an increase in acute phase parameters. The easiest form is a family cold urticaria. This syndrome is characterized by episodes of fever, urtikaropodobnyh rashes against the background of joint pain and general malaise. Interestingly, for the development of an attack, adult patients with FCAS simply have, for example, in the department with cooling products in the store. As a rule, the disease worsens the quality of life, but does not significantly affect its duration and the development of irreversible organ changes.

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In patients with MWS, in addition to the described manifestations, there are hearing impairments (sensorineural hearing loss), vision (uveitis, conjunctivitis), risk of amyloidosis (up to 25%), delay in physical and sexual development, and a decrease in life expectancy. Unlike FCAS, episodes of fever increase are often spontaneous and do not have a strict connection with hypothermia, acute phase parameters remain, as a rule, elevated even on days when fever and exanthema are absent [12].

CINCA/NOMID syndrome is the most severe form of CAPS, it manifests itself practically from the moment of birth, or in infancy, and is accompanied by multiple organ damage, high risk of amyloidosis, significant lag in physical and sexual development, influence on quality of life and a significant reduction in its duration [13-15]. In the clinical picture of the disease, fever, urtikaropodobnye rashes, an increased level of acute phase parameters of inflammation are constantly present. Patients with CINCA/NOMID syndrome have typical dysmorphic face changes, bone lesions in the form of local tumor-like hypertrophy [16,17]. Among organ manifestations, chronic meningitis should be noted, accompanied by signs of increased intracranial pressure (headache, morning vomiting, skull change, ventriculomegaly), as well as intellectual disorders of varying severity associated with brain tissue atrophy [14,17]. Also significant are hearing impairment (sensoneural hearing loss), vision (uveitis, conjunctivitis, papilloids), up to severe vision loss, if the disease is not diagnosed on time and the child does not receive adequate therapy [14].

CAPS has an autosomal dominant type of inheritance, respectively, similar symptoms or some of them may be present in the relatives of the patient. In most cases, in patients with typical CAMD Symptoms, mutations are localized in the 3 exon of the NLRP3 gene, responsible for the synthesis of the protein fragment necessary for the oligomerization process [18]. Approximately 16% of children with CAPD mutations are sporadic (de novo) and about 60% do not show any classical mutations. In patients with non-classical CAPS (for example, without exanthema) mutations can be localized in the 4 or 6 exon of the NLRP3 gene [19,20]. Up to 60% of patients with classical CASP phenotypes do not have mutations that can be identified by Sanger sequencing [21]. At present, this phenomenon can be explained by the presence of somatic mosaicism, when not all cells of the body have a mutation [22] or a genomic copy, when mutations in different genes can be manifested in a similar clinical picture.

Interest in the NLRP12 gene as a causative factor of fever arose due to the fact that individuals with undoubted syndrome FCAS did not show mutations in the NLRP3 gene. In 2008 I. Jeru et al. [23] reported three cases of NLRP12-associated disease in children. Two twin brothers who fell ill in the first month of life had episodes of fever, hearing loss, arthralgia and myalgia, while the level of CRP remained normal. They detected a mutation of p.Arg284X in exon 3 of the NLRP12 gene in the heterozygous state. In another case, in a 9 year old girl, fever arose at the age of 1 year, accompanied by abdominal pain, vomiting, lymphadenopathy and aphthous stomatitis, an increase in the level of CRP during the attack. The patient had a heterozygous mutation c.2072 + 3insT in the NLRP12 gene. Several members of the same family, especially those sensitive to cold, found the missense mutation p.D294E in the NLRP12 gene. In the carriers of this mutation, on contact with the cold, myalgia and arthralgia developed, whereas fever and exanthema were absent [24]. A mutation of p.Trp408X in the NLRP12 gene wasdetected in a family of 18 people who suffered very short attacks of fever and urticaroid-like rash of no more than 12-24 h [25]. Symptoms were stopped on their own, without the use of medication. In connection with the similarity of the clinical picture in patients with a mutation in the gene NLRP12 with that in patient with familial cold urticaria it is suggested to call this disease a family cold type II urticaria.

In most cases, NSAIDs and short courses of glucocorticoid therapy are effective in patients with NLPR12-associated syndrome. In the literature, I met a description of one case where a child with a family cold urticaria who did not have a mutation in the NLRP3 gene received an anakin therapy to stop seizures during the cold season. In another patient, the disease was accompanied by a delay in physical development, which was eliminated against the background of the use of the blocker IL1 kanakinumab, which indicates a significant effect of systemic inflammation on the child's body.

## CONCLUSION

In some cases, NLRP12-periodic syndrome in the clinical picture resembles a family cold urticaria, in the presence of certain mutations - MWS. In other cases, it has the features of an undifferentiated autoimmune syndrome. The search for mutations in the NLRP12 gene should be performed in patients with a clinical picture of familial cold urticaria and MWS syndrome that do not have mutations in the NLRP3 gene, as well as in all other cases of non-classical AIDS flow.

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