CASE REPORT

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Cryopyrin-Associated Periodic Syndrome

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Abstract: **Cryopyrin-associated periodic syndromes (CAPS) are characterized by apparently unprovoked attacks of fever, rashes, and musculoskeletal and sensorineural inflammation accompanied by high acute-phase reactants. Excessive interleukin-1 (IL-1) signaling appears to be a constant feature in the pathomechanism of the disease, driven by a gain-of-function mutation in the NLRP3 gene. Herein, we present the case of a 9-month-old boy with recurrent nonpruritic rashes and episodes of fever. The difficulties of early diagnosis due to initially mild clinical symptoms and the dramatic response to anti-IL-1 therapy after diagnosis emphasize the practical relevance of considering CAPS as a differential diagnosis in these patients.**

Hereditary autoinflammatory diseases describe an expanding group of conditions affecting the innate immune system leading to apparently unprovoked inflammation with fever, cutaneous and musculoskeletal involvement. Cryopyrin-associated periodic syndromes (CAPS) are characterized by mutations in the NLRP3 gene with constitutive activation of the inflammasome, which results in high levels of interleukin-1β (IL-1β), the major cytokine in the pathomechanism.

CASE PRESENTATION

A 9-month-old boy presented with a 5-month history of recurrent fever and nonitching, urticaria-like rashes (Fig. 1). Laboratory examination revealed elevated levels of C-reactive protein (CRP; 6.5–10.0 mg/dL) and a high erythrocyte sedimentation rate (ESR: 1 hour, 45–67 mm). All other parameters, including complete blood cell count, electrolytes, hepatic and renal laboratory parameters, serum immunoglobulin (Ig)E, antinuclear antibodies, antineutrophil cytoplasmic antibodies, immunoglobulin counts, complement and rheumatoid factors, antistreptolysin titer, and serum amyloid A were within normal limits on several occasions.

The family history was unremarkable, and the child was not affected in growth or development. Diagnosis of chronic urticaria was assumed and therapy with systemic antihistamines and antipyretics was initiated; however, the symptoms remained unchanged.

Eight months later the patient developed aseptic arthritis of his left knee and recurrent episodes of headache. Magnetic resonance imaging examinations and lumbar puncture with examination of cerebrospinal fluid (CSF) revealed aseptic meningitis (opening pressure 40–45 mm H_2O). A low-grade hearing loss was detected by audiometry.

The neonatal onset of apparently unprovoked generalized inflammation with chronic recurrent fever, urticarial skin rashes, aseptic arthritis, and aseptic meningitis is strongly indicative of CAPS. Thus, several molecular genetic examinations were performed, which disclosed a mutation within exon 3 of the *NLRP3* gene. This mutation

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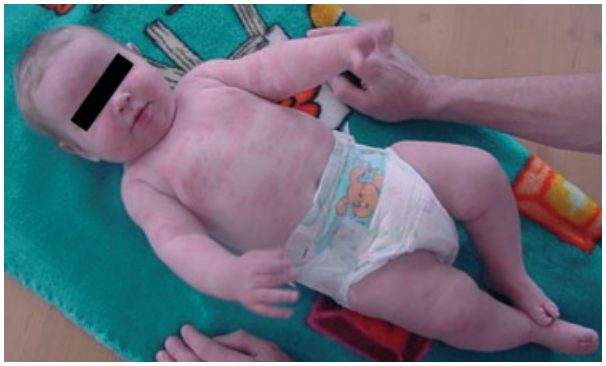

Figure 1. Nine-month-old infant with generalized nonpruritic, urticaria-like rash.

has been described as a characteristic and diagnostic molecular feature of Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS) (1).

At the age of two years, treatment with anakinra, a recombinant interleukin-1 (IL-1) receptor antagonist in a dosage of 2 mg/kg of body weight daily was established. Within days, fever episodes and urticarial rashes ceased, aseptic arthritis and aseptic meningitis resolved, and CRP levels and ESR levels normalized.

To date, after 5 years of effective therapy, no decrease in drug efficacy and no adverse effects except slight injection site reactions were noticed.

DISCUSSION

CAPS are a group of rare hereditary autoinflammatory syndromes that commonly display a gain-of-function mutation in the *NLRP3* gene encoding for cryopyrin (2). In the cytoplasm, cryopyrin interacts with several other proteins (ASC, CARDINAL, and procaspase 1) to form the inflammasome. This complex activates caspase-1 and subsequently results in cleavage of pro-IL-1 to its active form IL-1β (Fig. 2) (3). Cryopyrin is expressed in neutrophils, monocytes, and chondrocytes (4). The exact pathomechanism leading to neurologic symptoms in CAPS needs to be fully characterized. Reports indicate sensorineural hearing loss due to cochlear inflammation in up to 60% of patients with MWS, resulting in atrophy of the cochlear nerve in the long term (5). Little is known about intracranial inflammation, with reports showing high cytokine levels and numbers of neutrophils in CSF (6).

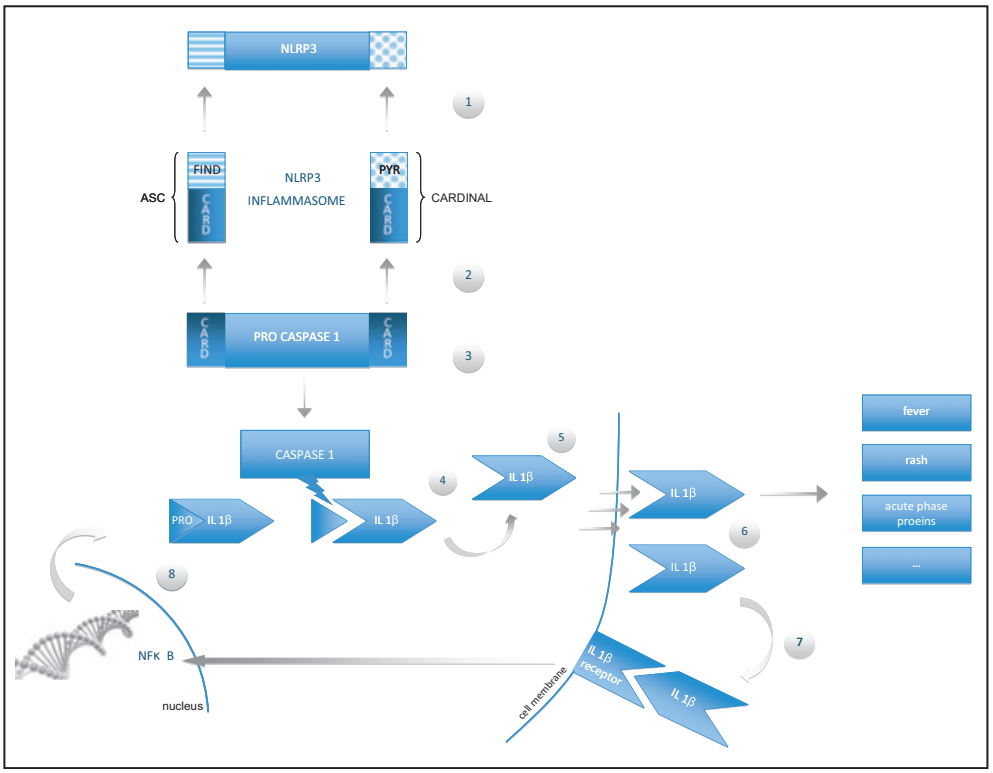

Figure 2. Pathomechanism in cryopyrin-associated periodic syndrome: Hereditary activation of NLRP3 (i) results in binding to components of the NLRP3 inflammasome (adaptor proteins ASC, CARDINAL, and procaspase 1) (ii) leading to its activation. Release of caspase 1 (iii) catalyses the cleavage of pro-interleukin (IL)-1β to its active form IL-1β (iv), which is liberated from the cell (v) and drives the inflammatory process (vi). IL-1β also binds to corresponding IL-1β receptors (vii), initiating a positive feedback loop. Downstream signaling pathways interact with nuclear factor kappa B (NFκB) and induce upregulation of pro-IL-1β transcription (viii) (3).

Clinically, CAPS can appear as three phenotypes: FCAS being a moderate form, MWS being an intermediate type, and neonatal-onset multisystem inflammatory disease (NOMID) being the most severe form (7).

Several other autoinflammatory syndromes with different genetic backgrounds, such as familial Mediterranean fever and pyogenic sterile arthritis with pyoderma gangrenosum and acne and pediatric granulomatous arthritis are also characterized by molecular changes affecting the innate immune system. Most of them display typical characteristics and can be differentiated clinically; however, molecular genetic examination is required for diagnosis and to enhance the knowledge of the genetic background in autoinflammatory syndromes (8,9).

Our patient displayed symptoms and a mutation characteristic for MWS, but aseptic meningitis is more often a symptom of the NOMID variant. Clinical overlaps for MWS and NOMID have been reported previously (7). Although genetic examination confirmed the diagnosis of MWS in our patient, mutations of *NLRP3* can be absent in up to 40% of cases with clinical CAPS (6,10).

Levels of acute-phase proteins such as CRP and serum amyloid A (SAA) are frequently elevated in CAPS. High titers of SAA may lead to systemic amyloidosis affecting approximately 25% of patients as a long-term complication predominantly involving the kidneys (7,11). Thus, early diagnosis and therapy is crucial for preventing organ damage. As with our patient, inflammatory markers can be normal in up to 25% of patients with MWS, indicating the possibility of additional, not-yet-identified (genetic) factors (7,12).

Skin manifestations of CAPS are an important key to early diagnosis. Rashes are typically nonitching, urticaria-like eruptions that persist in the same location for longer than 24 hours. These clinical findings can help to distinguish CAPS from various types of acute and chronic urticaria. Additional tests such as the ice cube test (for cold contact urticaria), pressure challenge test (for pressure urticaria), or the skin prick and radioallergosorbent tests facilitate excluding physically and (non) immunologically induced urticaria. Histology, which reveals a dermal neutrophilic infiltrate, excludes urticaria vasculitis. Although the true pathomechanism of the skin rash is not known, it is most likely secondarily induced by IL-1β released from neutrophils.

Other differential diagnoses of CAPS and MWS are systemic onset juvenile idiopathic arthritis (Still disease) and the Schnitzler syndrome. Whereas Still disease may also present with polyarthritis, fever episodes, and nonpruritic skin rash, the rash is usually salmon colored and characterized by a reticular distribution pattern. Schnitzler syndrome is rare in children (mean onset of disease 51 yrs). Moreover, the diagnosis requires monoclonal gammopathy (IgM) (13).

Similar to CAPS, the recently described autoinflammatory syndrome deficiency of the interleukin-1-receptor antagonist (DIRA) also results in enhanced IL-1 signaling. The distinct phenotype of DIRA with fetal distress, cutaneous pustulosis, oral mucosal lesions, bone and joint manifestations, and the absence of fever episodes allow the differentiation from CAPS clinically (14).

Antihistamines are ineffective in MWS since the urticaria-like rash is not driven by mast cell degranulation and the release of histamines. Several immunosuppressive and immunomodulatory agents have been used to control persistent inflammation including intravenous immunoglobulin, methotrexate, azathioprine, thalidomide, and colchicine (15). Long-term use of most of these medications is not feasible by reason of limited response or unfavorable side effects. Corticosteroids have some effect on disease severity and may be used temporarily in acute episodes.

New therapeutics target IL-1, which is assumed to be the leading cytokine involved in disease activity. Anakinra, a recombinant IL-1 receptor antagonist is administered daily using subcutaneous injection and has been considered a safe and effective treatment (16). Alternatively, new biologics with a longer half-life such as rilonacept, a dimeric fusion protein injected weekly and canakinumab, a human monoclonal antibody targeting IL-1β, have been successfully used in the

TABLE 1. *Characteristics of Current Drugs Targeting IL-1 Signaling in CAPS*

Active component	Brand name	Characteristics	Target	Half-life period	Administration
Anakinra	Kineret	Recombinant IL-1 receptor antagonist	IL-1α + β	4–6 hours	Daily sc
Rilonacept	Arcalyst	Fusion protein: extracellular domain of human IL-1 receptor and FC-domain of human IgG1	IL-1α + β	6.3 days (children) 8.6 days (adults)	Weekly sc
Canacinumab	Ilaris	Human monoclonal antibody	Selective IL-1β	22.9–25.7 days	Every 6–8 weeks sc
Under Investigation					
Gevokizumab (XOMA-052)	–	IgG2 humanized monoclonal antibody	Selective IL-1β	23 days	Monthly sc
VX765	–	Selective ICE/caspase-1 inhibitor	ICE/caspase-1	–	Orally

sc, subcutaneous; IL-1, interleukin-1; ICE, interleukin-converting enzyme.

treatment of CAPS (Table 1). Canacinumab has a half-life of 23–26 days in children and leads to sustained control of symptoms using subcutaneous injections every 8 weeks (17).

Summarizing our data, we present a young patient whose clinical symptoms were misinterpreted initially. Only additional symptoms such as aseptic arthritis or meningitis contributed to the clinical diagnosis of CAPS, supported by complementing molecular genetic examinations. As in this case, early recognition can be challenging. We suggest considering the differential diagnosis of CAPS for children with recurrent, nonpruritic, urticaria-like rashes and relapsing fever episodes. Rapid initiation of interleukin-1 antagonist therapy is a prerequisite for successful long-term outcome.

REFERENCES

1. Dodé C, Le Dû N, Cuisset L et al. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. Am J Hum Genet 2002;70:1498–1506.
2. Hoffman HM, Mueller JL, Broide DH et al. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet 2001;29:301–305.
3. Lachmann HJ, Quartier P, So A et al. The emerging role of interleukin-1β in autoinflammatory diseases. Arthritis Rheum 2011;63:314–324.
4. Feldmann J, Prieur AM, Quartier P et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet 2002;71:198–203.
5. Montealegre Sanchez GA, Hashkes PJ. Neurological manifestations of the Mendelian-inherited autoinflammatory syndromes. Dev Med Child Neurol 2009;51: 420–428.
6. Stojanov S, Weiss M, Lohse P et al. A novel CIAS1 mutation and plasma/cerebrospinal fluid cytokine profile in a German patient with neonatal-onset multisystem inflammatory disease responsive to methotrexate therapy. Pediatrics 2004;114:124–127.
7. Leslie KS, Lachmann HJ, Bruning E et al. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. Arch Dermatol 2006;142:1591–1597.
8. Church LD, Cook GP, McDermott MF. Primer: inflammasomes and interleukin 1beta in inflammatory disorders. Nat Clin Pract Rheumatol 2008;4:34–42.
9. Braun-Falco M, Ruzicka T. Skin manifestations in autoinflammatory syndromes. J Dtsch Dermatol Ges 2011;9:232–246.
10. Goldbach-Mansky R, Kastner DL. Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. J Allergy Clin Immunol 2009;124:1141–1149.
11. van der Hilst JC, Simon A, Drenth JP. Hereditary periodic fever and reactive amyloidosis. Clin Exp Med 2005;5:87–98.
12. Wittkowski H, Kuemmerle-Deschner JB, Austermann J et al. MRP8 and MRP14, phagocyte-specific danger signals, are sensitive biomarkers of disease activity in cryopyrin-associated periodic syndromes. Ann Rheum Dis 2011;70:2075–2081.
13. Lipsker D. The Schnitzler syndrome. Orphanet J Rare Dis 2010;5:38.
14. Aksentijevich I, Masters SL, Ferguson PJ et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med 2009;360:2426–2437.
15. Kallinich T, Hoffman HM, Roth J et al. The clinical course of a child with CINCA/NOMID syndrome improved during and after treatment with thalidomide. Scand J Rheumatol 2005;34:246–349.
16. Kuemmerle-Deschner JB, Tyrrell PN, Koetter I et al. Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome. Arthritis Rheum 2011;63:840–849.
17. Kuemmerle-Deschner JB, Ramos E, Blank N et al. Canakinumab (ACZ885, a fully human IgG1 anti-IL-1β mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS). Arthritis Res Ther 2011;13:R34.