Successful Treatment of CINCA/NOMID Syndrome with Interleukin-1 Blockade

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KEY WORDS: CINCA/NOMID syndrome, autoinflammatory syndrome, NALP3 mutation, biological therapy, anakinra, canakinumab, interleukin (IL)-1 blockade

IMAJ 2015; 17: 389–391

Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autosomal dominant hereditary autoinflammatory syndromes induced by overproduction of pro-inflammatory cytokine interleukin-1β (IL-1ß). CAPS comprises three syndromes: i) familial cold autoinflammatory syndrome (FCAS), ii) Muckle-Wells syndrome (MWS), and iii) chronic infantile neurological, cutaneous and articular/multisystem inflammatory disease beginning in the newborn period syndrome (CINCA/NOMID) [1]. The pathogenesis of these diseases includes some of the > 70 known mutations in the *NALP3* gene encoding the NALP3 protein (cryopyrin). This protein, a constituent of the multiprotein complex called inflammasome, plays an important role in both physiological and pathological immune responses. The activation of NALP3 leads to the activation of the caspase 1 enzyme, which cleaves the pro-IL-1ß molecule, allowing the release of biologically active IL-1ß into circulation [1]. While FCAS and MWS are characterized by moderate clinical manifestations, the CINCA/NOMID syndrome is the most severe form of cryopyrinopathies [1,2]. IL-1β exerts pleiotropic effects. In the bone marrow, it stimulates mobilization of granulocyte progenitors and mature neutrophils. This cytokine promotes breakdown of cartilage and bone resorption. IL-1ß also increases production of the pro-inflammatory cytokine IL-6 by endothelial cells, which leads to production of acute-phase proteins, such as C-reactive protein (CRP) and serum amyloid A (SAA) in the liver [2].

The *NALP3* gene is located on chromosome 1q44. Mutations in this gene lead to varying degrees of seemingly unprovoked (autoinflammatory) overproduction of IL-1ß, which is crucial in the pathogenesis of cryopyrinopathies and determines the range and intensity of clinical manifestations in these syndromes [1].

The clinical picture of autoinflammatory syndromes may vary from disease to disease. The most common symptoms include fever, fatigue, urticarial rash, conjunctivitis, headache resulting from aseptic meningitis, and arthralgias/arthritis. The first symptoms become evident in the neonatal period. The persistence of inflammation gradually leads to central nervous system (CNS) damage, loss of visual acuity, progressive sensorineural hearing loss, and mental retardation. The long-term consequences also include arthropathy, which affects joint function. The prognosis of patients, however, depends on the development of amyloidosis, which causes kidney failure and premature death in about 25% of patients [1].

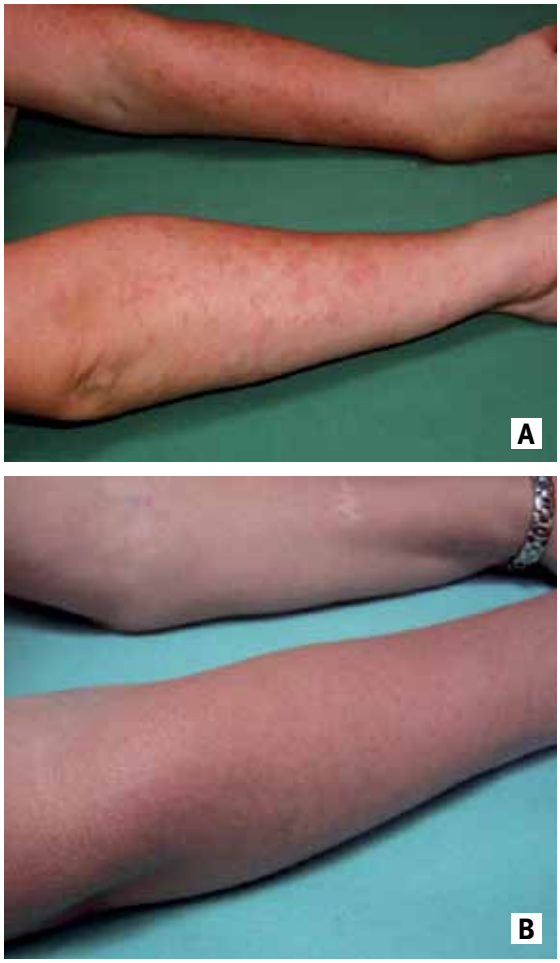
With regard to treatment, non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, immunosuppressive disease-modifying antirheumatic drugs (DMARDs) and tumor necrosis factor-alpha (TNFα) inhibitors only partially reduce the clinical symptoms [1,2]. Based on current understanding of the NALP3 inflammasome and IL-1β as well as their role in the pathogenesis of autoinflammation, the introduction of IL-1 blockade has led to new therapeutic horizons [2]. We present here a case of CINCA/NOMID syndrome in a 33 year old woman.

PATIENT DESCRIPTION

In this patient the first symptoms of the disease – fever and urticarial rash – occurred already in her first week of life. Urticaria was most pronounced on the trunk, face and upper limbs. Laboratory markers of inflammation were elevated (erythrocyte sedimentation rate 100 mm/hr, CRP 69 mg/L). This was accompanied by leukocytosis with a predominance of polymorphonuclear leukocytes. Tradtional treatment, including NSAID, antihistamines, and repeated courses of antibiotics or systemic corticosteroids, was ineffective. In addition to fever, other symptoms developed, such as erythema, arthralgia and headache, loss of visual acuity and hearing loss, which gradually worsened. Pain and swelling of joints appeared when she was 3 years old, headache and lymphadenopathy at age 4, aseptic meningitis at age 8, and ocular complications including uveitis, edema of the optic nerve, and gradual hearing loss at age 11 years. Targeted genealogical research did not find similar disease in any other member of the family. The patient's only sibling (female) is healthy.

Based on the clinical picture, laboratory findings and the characteristic disease course, CINCA syndrome was diagnosed.

Figure 1. Skin rash in our CINCA/NOMID patient before **[A]** and 7 days after **[B]** anakinra treatment



Genetic analysis performed in a foreign laboratory confirmed the T405P de novo *NALP3* gene mutation [1]. Since all the above described symptoms persisted, together with progressive loss of visual acuity and hearing, and considering earlier reports on the efficacy of IL-1 blockade in childhood autoinflammatory syndromes including MWS and FCAS [1,2], we initiated anakinra treatment. The patient at this point was 25 years old. Anakinra was administered subcutaneously at a dose of l00 mg/day. Already within the first week of treatment we observed a dramatic amelioration of symptoms and decrease in acute-phase reactant levels [Figure 1]. After 6 months of treatment, most of the symptoms (fever, headache, arthralgia and rash) disappeared completely; however, hearing loss still persisted and examination confirmed 82% hearing loss.

In 2011, the anti-IL-1 antibody canakinumab was registered for the treatment of autoinflammatory syndromes. Our patient needed life-long administration of biologics and since daily administration was difficult to manage by herself, in April 2011 we switched to canakinumab, which is administered once every 8 weeks. The patient tolerated this treatment well, but 2 weeks before each injection she experienced severe headache and arthralgias. These symptoms were not attributed to adverse effects of treatment but rather to the limited efficacy of canakinumab. Therefore, after discussions with the patient, we returned to the treatment with anakinra, which has been ongoing for 8 years to date. The patient is subjectively well, has no fever, rash, arthralgia or ocular symptoms; however, her hearing loss persists.

Treatment was well-tolerated and only mild urogenital infections occurred, which responded well to standard treatment. She has normal renal function and no clinical signs of amyloidosis. Her concentration of SAA (13.9 mg/L) exceeds the upper limit of the reference range (6.4 mg/L). The pretreatment level of SAA is unknown because the SAA test was unavailable at that time. Thus, we will closely monitor her renal function and repeatedly assess SAA levels.

COMMENT

We have described the case of a 33 year old woman with CINCA/NOMID syndrome that developed soon after birth. Although the first symptoms of the disease occurred already in her first year of life, targeted therapy became available only when she was 25. Despite the relatively late start of biological treatment, most of her symptoms abated dramatically and she experienced a significant positive improvement in the quality of life. Anakinra was effective and well tolerated; however, due to compliance issues, we switched to canakinumab but its efficacy was limited. Repeated introduction of anakinra maintains an almost symptom-free status; however, none of the IL-1 inhibitors had any effect on the persistent hearing loss.

Our results are similar to those reported by other investigators. In 2006 Goldbach-Mansky et al. [3] published the first results on the efficacy of anti-IL-1 treatment in autoinflammatory syndromes. They recorded rapid regression of clinical and laboratory signs of disease, including decrease in serum CRP and SAA levels in 18 patients with CINCA/NOMID syndrome. In that cohort the mean age was 11 years. After 3 months of treatment, biologics were interrupted and the symptoms recurred in all children, indicating that long-term treatment was needed. Repeated treatment was successful in ameliorating symptoms, and these beneficial effects were maintained throughout the 6 months of follow-up.

Amyloidosis often leading to renal failue and early death may be a frightening long-term consequence of autoinflammatory syndromes. The development of amyloid deposits is associated with sustained elevation of CRP and SAA levels. Amyloid deposition may occur in almost 25% of patients. In a cohort of 372 patients with amyloidosis and renal impairment, Lachmann and colleagues [4] demonstrated a strong association between mortality and SAA levels, as well as regression of amyloid deposits after normalizing SAA concentrations. Due to the efficacy of the treatment in our patient, she has normal renal function and no clinical signs of amyloidosis. However, as described above, her SAA levels are somewhat elevated and will require close monitoring. Also, deforming arthropathy did not develop. Once joint destruction develops, it is very difficult to reverse, even with biological treatment [4].

Although anakinra treatment was considered effective in our patient, we were unable to arrest the progression of hearing loss. This observation is also consistent with published data. Lepore et al. [5] reported improvement in sensorineural hearing loss in only one of seven children treated with anakinra. The most likely cause of inefficacy in our patient was the late initiation of treat-

ment; she was 25 when irreversible hearing loss was already present.

Anakinra treatment was well-tolerated by our patient. During the 8 year treatment period we did not observe any major complications that required hospitalization. In the second year of treatment, urinary tract infections developed which were treated by antibiotics. After 8 years of treatment, the clinical reponse is still favorable with no notable adverse events.

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References

1. Church LD, Cook GP, McDermott MF. Primer: inflammasomes and interleukin 1beta in inflammatory disorders. *Nat Clin Pract Rheumatol* 2008; 4 (1): 34-42.
2. Dinarello CA. Blocking IL-1 in systemic inflammation. *J Exp Med* 2005; 201 (9): 1355-9.
3. Goldbach-Mansky R, Dailey NJ, Canna SW, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. *N Engl J Med* 2006; 355 (6): 581-92.
4. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; 356 (23): 2361-71.
5. Lepore L, Paloni G, Caorsi R, et al. Follow-up and quality of life of patients with cryopyrin-associated periodic syndromes treated with Anakinra. *J Pediatr* 2010; 157 (2): 310-15 e1.