

## Letters to the Editor

### Dramatic improvement with anakinra in a case of chronic infantile neurological cutaneous and articular (CINCA) syndrome

SIR, Chronic infantile neurological, cutaneous and articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID), is a rare genetic systemic auto-inflammatory disease characterized by mutation in the *CIAS1* (cold autoinflammatory syndrome-1) gene [1, 2]. Renal AA-amyloidosis, severe arthropathy and neurological complications are long-term disabilities with this disease. CINCA syndrome is poorly treatable and steroids do not completely eliminate the disease and can cause harmful side-effects. We report a case of CINCA syndrome which was dramatically improved with anakinra, an interleukin-1-receptor antagonist (IL1-RA).

In 2002, a 36-yr-old man consulted for a diagnosis of Muckle-Wells syndrome (MWS). He had suffered from birth from a generalized urticarial skin lesion with episodes of fever and conjunctivitis. He complained of arthritis which was particularly severe during childhood and involved knees, ankles and wrists, and required long-standing steroid treatment. He developed progressive sensorineural deafness and required bilateral prosthesis at the age of 15. He also suffered from mild mental retardation and left school early. Headaches related to chronic meningitis with papilloedema were diagnosed during childhood. Numerous blood tests throughout his life had revealed persistent massive neutrophilia, anaemia and intense acute phase response. No proteinuria was found. Faced with urticarial skin lesion, fever and deafness, an initial diagnosis of MWS was made during childhood. However, when we met the patient we noticed a dysmorphic facial appearance characterized by frontal bossing of the skull, saddle nose, micrognathia and clubbing of the fingers. After genetic advice, a diagnosis of CINCA syndrome was made which could explain the dysmorphic appearance, the mental retardation and the chronic meningitis with papilloedema—all classical features of this syndrome [3]. Sequencing of *CIAS1* revealed that the patient was heterozygous for the D303N mutation in exon 3. At the time of this result in 2002, *CIAS1* gene analyses in CINCA syndrome had not yet been published but were published soon afterwards [1, 2]. The patient used to be treated with steroids when crises were severe, but only a high dose (1 mg/kg) could decrease the level of inflammation. At the time we met the patient, the steroid dose was 10 mg/day. Colchicine was added with celecoxib (200 mg/day). However, the patient still had arthritis of wrists, knees and ankles, urticarial rash and fatigue. Biological evaluation in May 2004, immediately

before the institution of anakinra treatment, revealed a severe inflammatory process (Table 1). The patient was informed of the therapeutic trial and subcutaneous anakinra (100 mg/day) was started in May 2004. At the same time, celecoxib was discontinued. Within 1 week of commencement of treatment he noted a dramatic clinical change: fatigue, rash, conjunctivitis and arthralgia had disappeared. Steroids were progressively tapered and discontinued in June 2004. Follow-up at 6 months showed a persistent good response to anakinra; the patient felt very well and only had one mild flare with fever and arthralgia which regressed with analgesic treatment and did not require steroids. He no longer complained of asthenia and headaches, and urticarial rash did not occur. He was able to play badminton once a week without any articular complaint. His friends and mother clearly noticed the improvement in health. Biological evaluation showed a regression of the inflammatory process (Table 1). Anakinra treatment was tolerated very well and the initial dose was maintained.

The two other autoinflammatory syndromes related to *CIAS1* mutations are MWS and familial cold autoinflammatory syndrome (FCAS) [4, 5]. All three syndromes have some common features such as fever, urticarial rash, biological inflammatory process and risk of renal amyloidosis but also have different characteristics: cold triggering for FCAS and articular, neurological and dysmorphic symptoms in CINCA syndrome. *CIAS1* encodes a member of the pyrin superfamily of death domain fold proteins called 'cryopyrin' that is involved in inflammation and apoptosis. It is expressed in polymorphonuclear cells, monocytes, chondrocytes and activated T cells [1, 6]. Cryopyrin has been shown to be an activator of caspase 1 that cleaves pro-IL-1 $\beta$  into biologically active IL-1 $\beta$  and has been shown to activate NF- $\kappa$ B [7]. Thus, a hypothesis explaining the inflammatory events in CINCA syndrome involves a hyperactive state with release of IL-1 $\beta$  and influx of polymorphonuclear cells to the site of inflammation. Moreover, high secretion of IL-1 $\beta$  by peripheral blood cells, spontaneously and after stimulation, has been evidenced in CINCA syndrome [8]. Thus treatment with anakinra is particularly interesting in CINCA syndrome as it targets the main cytokine involved in the inflammatory process. Dramatic response to anakinra in CINCA syndrome has already been observed, similar to our observation, by Hawkins *et al.* [9], and was initially reported in three cases of MWS [10]. Thus anakinra therapy is warranted in patients with inflammatory disorders associated with mutation in *CIAS1*, but physicians must be aware of the increased risk of infection associated with this drug.

TABLE 1. Biological evolution before and after anakinra treatment

Data	January 2004	May 2004	August 2004	September 2004	December 2004
White blood cell count ( $10^9/l$ )	13.7	21.5	10.4	13	8.8
Haemoglobin level (g/dl)	12.4	12.3	15.7	15.8	15.4
Platelet count ( $10^9/l$ )	429	425	246	267	308
C-reactive protein (mg/l, $n < 5$ )	102	57	6	13	15
Anakinra 100 mg/day	No	Yes (start in May)	Yes	Yes	Yes
Steroid (mg/day)	10	Progressive tapering and discontinued in June 2004	No	No	No
Celecoxib (mg/day)	200	No	No	No	No
Colchicine (mg/day)	1	1	1	1	1

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