Positive clinical and biochemical responses to anakinra in a 3-yr-old patient with cryopyrin-associated periodic syndrome (CAPS)

Sir, Cryopyrin-associated periodic syndromes (CAPS) consist of a subgroup among hereditary periodic fever syndromes that includes familial cold-induced autoinflammatory syndrome (FCAS; MIM no. 120100), Muckle–Wells syndrome (MWS; MIM no. 191900) and chronic infantile neurological, cutaneous, articular (CINCA) syndrome (MIM no. 670115), also known as neonatal-onset multisystem inflammatory disease (NOMID), representing different degrees of disease severity. All of them have been recently associated with heterozygous mutations in the CIAS1/PYPAF1/NALP3 gene, which encodes the cryopyrin protein [1, 2]. This protein was found to be a constituent of inflammasome, an intracellular multiprotein complex involved in the cleavage and activation of proinflammatory cytokines IL-1β and IL-18 [3].

Here we present the case of a 3-yr-old male patient, without a familial history of periodic fever, diagnosed with possible MWS. His symptoms began when he was 9 months old, and consisted of long inflammatory episodes, recurring every 4–6 weeks, characterized by high fever, urticarial rash, abdominal pain, headache and irritability secondary to mild chronic aseptic meningitis, conjunctivitis, arthralgia, arthritis and occasionally diarrhoea. Neither reactive AA-type amyloidosis nor sensorineural deafness were present. A strong acute-phase response, with important elevation of C-reactive protein (CRP) and serum amyloid (SAA-1) protein, was detected in all these episodes (Fig. 1).

The diagnosis of CAPS was confirmed by the detection of the de novo heterozygous T348M mutation in the CIAS1/PYPAF1/NALP3 gene, as has been previously reported [4].

Non-steroidal anti-inflammatory drugs and corticosteroid treatment administered before CAPS diagnosis gave a negative response. Therefore, taking in account previous experience of treatment in adult patients with MWS and CINCA/NOMID syndrome [5–7], we started a therapeutic approach with anakinra, the human recombinant interleukin (IL)-1 receptor antagonist (Kineret; Amgen), that inhibits the pro-inflammatory IL-1 signaling pathway. This treatment was initiated during an inflammatory episode by means of subcutaneous injections, in doses of 1 mg/kg/day. The patient was hospitalized for the first week to detect any of the possible side-effects, and afterwards we maintained an ambulatory routine for 4 weeks, monitoring the clinical and biochemical responses weekly. Eventually, we established periodical controls every 2 weeks. A positive clinical response was detected, with a complete disappearance of skin rash, irritability, periodic fever, conjunctivitis and abdominal pain at 24 h after the first injection, and joint involvement at 48 h. The strong acute-phase response resolved during the first week of treatment, decreasing noticeably the plasma levels of acute-phase reactants. These positive clinical and biochemical responses have persisted during 9 months of follow-up (Fig. 1). No side-effects have been identified. An attempt to reduce the anakinra dose to 0.75 mg/kg/day was unsuccessful, due to the appearance of low fever (37.5°C), headache and discomfort. When the initial dosage was reinstated these symptoms disappeared.

The most severe complications that have been described in patients with MWS are reactive AA-type amyloidosis and progressive bilateral sensorineural hearing loss. The strong decrease and normalization of plasma levels of acute-phase reactants detected in this paediatric patient during continuous treatment with anakinra suggests to us a hopeful decrease in his risk of developing reactive AA-type amyloidosis, due to its relationship with the plasma levels of SAA-1 protein [8]. Longer clinical and biochemical follow-up would be necessary to establish this risk accurately. However, we are not able to state that these positive clinical and biochemical responses to anakinra might prevent the development of sensorineural deafness in the future.

Dierselhuis et al. [9] have recently suggested that intermittent administration of anakinra during acute episodes instead of continuous treatment could be a therapeutic approach in some recurrent autoinflammatory disorders. However, the appearance of some clinical symptoms during an attempt to reduce the anakinra dose in this patient, and the advisability of maintaining his plasma levels of acute-phase reactants at normal values, led us to think that continuous treatment is most convenient in this patient.

We think that it is worthwhile publishing this positive experience with anakinra, because other children with CAPS could benefit from this treatment. As Hawkins et al. [7] suggested, early and prolonged therapeutic trials with anakinra are warranted in patients with CAPS to establish its efficacy and possible side-effects during long-term treatments, and to know if the most severe complications of CAPS—CNS involvement, papilloedema, sensorineural deafness and deforming arthropathy—could be prevented.

Key messages

There was a positive response to continuous anakinra therapy in a paediatric CAPS patient.
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Running for gout research

Sir, The differential diagnosis of a swollen red forefoot includes acute gouty arthritis of the first metatarsophalangeal joint (MTPJ). This is confirmed following demonstration of sodium monourate crystals in synovial fluid or tissues. Classic risk factors include obesity, family history, diuretic use and historically high alcohol and purine-containing diets.

We describe a case of acute podagra in a young, athletic man. Our case reinforces important risk factors and we feel provides support for associated aetiology.

A 28-yr-old rheumatology Senior House Officer ran the 2003 London Marathon. Following completion of the 26.2 mile course he unsurprisingly complained of widespread myalgia and arthralgia. Despite this, his euphoria and thirst led him to a public house where he drank two pints of beer. He then returned home and continued his pre-marathon diet of foods rich in purine including nuts, crab and sardine sandwiches.

Over the next 2 days his right first MTPJ became increasingly painful. Unable to ignore his symptoms he asked his Specialist Registrar to investigate.

Blood results were normal except for creatinine kinase of 248 IU/l and C-reactive protein of 7 mg/l. Serum urate concentration was normal at 0.4 mmol/l and 24-h urine collection showed a normal renal output of urate. Plain X-ray confirmed soft tissue swelling around the first MTPJ. Joint aspiration yielded 2 ml of turbid synovial fluid. Polarized light microscopy confirmed negatively birefringent needles. The diagnosis of acute gout was confirmed and treated with non-steroidal anti-inflammatory drugs.

When investigating the causes of acute forefoot pain, one would not be immediately suspicious of gout in a young man. However, our case displayed a number of risks in that he was male and perhaps more significantly he was exposed to recognized predisposing factors including a high-purine diet and dehydration exacerbated by alcohol intake [1, 2].

Alcohol is associated with reduced renal excretion of urate by lactic acid production. It can also promote degradation of adenosine triphosphate (ATP) leading to increased formation of urate.

Despite this, gout remains relatively rare in males under the age of 30. It is well recognized that acute gout occurs in the presence of normal plasma uric acid in approximately 30% of cases. In our case urate was not measured at the time of onset of symptoms. The 24-h urine urate measurement excluded the possibility of under-excretion.

This led us to examine the possible role of severe physical exertion leading to muscle fatigue, tissue hypoxia and reperfusion injury. Case reports of gout precipitated by marathon running are rare. Moore and Anderson [3] reported a 33-yr-old male runner with knee and ankle pain complicated by an aortic valve nodule secondary to gout and visceral tophi. Studies have shown elevated plasma hypoxanthine and uric acid levels following prolonged exercise. The mechanism involves activation of adenylate kinase in muscle cells leading to degradation of adenosine nucleotides. This has been demonstrated consistently in anaerobic but also aerobic exercise, both conditions induced in distance running [4, 5]. A case study by Hellsten Westing et al. [6] confirmed high plasma hypoxanthine and urate levels and this correlated with increased running distance. Sutton et al. [7] demonstrated elevated plasma uric acid concentration in 11 subjects following a marathon run.

We feel that the additional factor of tissue hypoxia affecting the distal extremity of the first MTPJ triggered the cascade of ischaemia and reperfusion thus contributing to urate production. This mechanism may be exacerbated by foot stance. Our case had a high medial arch and ‘toe strikes’ when running thus potentiating the ischaemic insult directly onto the joint.

Hypoxia causes reduced ATP levels and inhibits fatty acid desaturation. This increases degradation of phospholipids and changes cellular permeability with calcium influx from extracellular and intracellular stores. In response calcium-dependent proteases are activated and this initiates the conversion of xanthine dehydrogenase (XDH) to xanthine oxidase (XO). Xanthine is catalysed to urate by XO [8]. Reperfusion increases oxygen concentration, leading to XO generating production of free radicals including superoxide, nitric oxide and hydroxide. These free radicals attack cell integrity by damaging DNA leading to cell death and this promotes the inflammatory process [8, 9].

In summary we feel our case illustrates multifactorial triggers including classic risk factors combined with hypoxic reperfusion