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CASE REPORT

Etanercept and anakinra can prolong febrile episodes in patients with hyperimmunoglobulin D and periodic fever syndrome

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Abstract Hyperimmunoglobulin D and periodic fever syndrome (HIDS) is a rare, hereditary autoinflammatory condition, characterized by recurrent inflammatory episodes. There is no proven treatment for HIDS, but various drugs including, non-steroidal anti-inflammatory drugs, colchicine, steroids, statins and thalidomide have all been tried. Recently, some patients have demonstrated a good clinical response to either etanercept or anakinra. We report a case of a 10-year-old girl who experienced prolonged and severe inflammatory attacks, when she was treated with etanercept, and later with anakinra.

Keywords Hyper IgD and periodic fever syndrome (HIDS) · Etanercept · Anakinra · Treatment · Adverse effects

Introduction

Hyperimmunoglobulin D and periodic fever syndrome (HIDS, OMIM #260920) is a rare autosomal recessive autoinflammatory syndrome. It is caused by mutations in the gene encoding mevalonate kinase (MVK), an enzyme involved in the isoprenoid and cholesterol biosynthesis pathway. Mutations result in reduced enzymatic activity. The most common mutation in HIDS is the V377I mutation [1]. The disease usually presents in infancy and is characterized by recurrent febrile episodes, lasting 3–7 days and recurring every 4–8 weeks. Febrile episodes are often associated with headaches, myalgia, arthralgia, abdominal pain, vomiting, diarrhoea, lymphadenopathy, splenomegaly, skin rashes and aphthous ulcers.

All patients elicit an acute-phase response during attacks, with leukocytosis, raised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum amyloid A (SAA). A polyclonal rise in serum IgD levels to greater than 100 KU/L is considered as the hallmark of HIDS. This is often associated with an increased serum IgA level.

Attacks can be precipitated by vaccination and minor infections. The disease tends to improve with age, as attacks become less frequent [2, 3]. Amyloidosis is a rare complication that has been reported in up to 2.9% of HIDS patients [3, 4].

A spectrum of clinical severity exists within patients with MVK deficiency. A complete deficiency of MVK causes mevalonic aciduria, which is characterized by microcephaly, psychomotor retardation, ataxia, myopathy, ocular involvement, failure to thrive, recurrent febrile episodes, and an acute-phase response, with elevated IgD and IgA levels [5].

There is no proven treatment for HIDS and randomized control trials are lacking. Corticosteroids have been effective in reducing the severity of attacks in some cases [6]. Colchicine, NSAIDS, statins, and thalidomide have been tried with variable responses [6–10].

More recently, the tumour necrosis factor-α (TNF-α) inhibitor, etanercept [3, 9, 11, 12], and the interleukin-1 receptor antagonist (IL-1Ra), anakinra [13–15] have both been successfully used in some patients with HIDS.

Case history

We present the case of a 10-year-old Caucasian girl with a history of recurrent febrile episodes, since 11 months of

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age. They typically occur every 3–4 weeks, last 3–4 days and are characterized by fever (up to 40°C), headache, arthralgia, and cervical lymphadenopathy. There is an associated neutrophilia, elevated ESR (up to 71 mm/h), CRP (up to 342 mg/L) and SAA (up to 961 mg/L). Bacterial and viral cultures during attacks have been consistently negative, and antibiotics have been ineffective in reducing the frequency and duration of the episodes. Inflammatory attacks have been triggered by viral infections and routine immunizations.

She is well between episodes, but is prone to frequent mouth ulcers. CRP, ESR and SSA levels are normal in-between episodes. Investigations revealed negative antinuclear antibodies, normal rheumatoid factor, normal IgG and IgM levels, but a persistently raised IgA level between 2.8 and 4.53 g/L (normal 0.5–2.5 g/L). Serum IgD level was more than 100 KU/L on two occasions, at 198 KU/L and 133 KU/L (normal 2–100 KU/L).

Molecular analysis revealed that she was compound heterozygous for HIDS, with two known mutations in the MVK gene. V3777I is a common substitution in HIDS. H380R is a known, but less common substitution.

She partially responded to a daily dose of 500 mcg of colchicine: febrile episodes occurred at the same frequency, but only lasted 1–2 days.

In order to control ongoing inflammation, and thus reduce the risk of amyloidosis, she was started on etanercept, in February 2008; 10 mg of etanercept was given twice weekly for 9 weeks. During that period, she had fortnightly episodes, two of which continued for more than 7 days. The first prolonged episode was triggered by gastroenteritis and lasted for 10 days. The second prolonged episode started 2 weeks later. At 7 days, she was still symptomatic, CRP was 234 mg/dl and ESR was 60 mm/h. Etanercept was stopped and her symptoms resolved within 2 days. She restarted colchicine 4 weeks later and continued to have minor episodes every 3–4 weeks. Episodes settled within 24–48 h. Increasing the colchicine dose to 1,000 mcg/day was complicated by abdominal discomfort and diarrhoea.

On the basis of case reports that suggested a good response to anakinra in some HIDS patients who have not responded to etanercept [14, 15], a trial of anakinra was considered. A daily dose of 100 mg of anakinra was commenced in November 2008. The patient had been suffering from a febrile episode for 2 days on the day anakinra was started. Inflammatory markers were raised: ESR and CRP were 53 mm/h and 155 mg/L, respectively. She continued to deteriorate, with fever up to 40°C, flu-like symptoms, pallor, cough, abdominal pain and cervical lymphadenopathy. Five days later, she was still symptomatic: ESR and CRP remained elevated at 55 mm/h and CRP 139 mg/L, respectively. Her parents felt that this represented one of her worst and most prolonged HIDS attacks. Anakinra was stopped and 3 days later, her symptoms resolved completely; CRP and ESR went down to 21.5 mg/L and 38 mm/h, respectively.

She was recommenced on 750 mcg colchicine and continues to have minor attacks every 4–6 weeks.

Discussion

HIDS is an autoinflammatory syndrome caused by mutations in the gene encoding MVK, an enzyme that plays a central role in the synthesis of cholesterol and isoprenoids [2]. The cause of the inflammatory attacks remains obscure. However, plasma levels of TNF-α and IL1 Ra, and the ex vivo production of TNF α and interleukin-1β by monocytes are raised during acute HIDS attacks [16]. These findings suggested etanercept and anakinra as potential therapies for HIDS patients.

There have been mixed reports on the effectiveness of etanercept in HIDS patients. Etanercept has been beneficial in reducing the severity and frequency of febrile episodes in some patients [3, 9, 11, 12], but was ineffective in others [3, 14, 17].

A few reports suggest that anakinra is beneficial [13] and may be more effective than etanercept, when used in patients with HIDS [14, 15]. Moreover, anakinra has been successfully used in two patients with complicated MVK deficiency. The first was an 18-month-old boy with the unusual complication of membranoproliferative glomerulonephritis. Treatment with anakinra resulted in improvement of his inflammatory episodes and resolution of glomerulonephritis [18]. The second case was that of a 32-year-old female with bilateral, destructive polyarthritis. Continuous treatment with anakinra resulted in disease resolution [19]. A recent study suggests that 80% of HIDS patients show some response to either to etanercept or anakinra [3].

Our patient not only failed to respond to these monoclonal antibodies, but febrile episodes became more frequent and prolonged when she was on etanercept. When anakinra was administered during an acute attack, HIDS symptoms became more severe and prolonged. The discontinuation of both etanercept and anakinra was associated with rapid clinical improvement and normalization of inflammatory markers. As the pathophysiology of HIDS is not well understood, it is difficult to explain this effect of etanercept and anakinra. It is possible that TNF-α and IL-1 blockade can result in persistence of minor infections, which can act as a triggers for HIDS attacks. Nevyjel et al. [18] have previously suspended the administration of anakinra in a HIDS patient who was responsive to anakinra, when a concomitant viral infection was suspected. To the best of our knowledge, this is the first report of

etanercept and anakinra resulting in prolongation and exacerbation of HIDS attacks.

Colchicine has been reported to be ineffective in HIDS [3, 6, 9], but the duration of our patient's attacks is currently reduced while she is on colchicine, suggesting that some HIDS patients may partially respond to the drug.

Conclusions

The treatment of HIDS remains difficult and effective treatment is currently sought on a trial and error basis. Most of the evidence available is on a small number of case reports. The recent literature suggests that etanercept and/or anakinra are effective therapies in most HIDS patients. However, the case we described suggests that these monoclonal antibodies may exacerbate and prolong acute attacks in a subgroup of HIDS patients.

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