CASE REPORT

Hyperimmunoglobulinaemia D syndrome: a rare cause of prolonged fever and treatment with anti-interleukin 1 agent

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SUMMARY

Hyperimmunoglobulinaemia D syndrome (HIDS) is an autosomal recessive, autoinflammatory disease that is characterised with intermittent febrile episodes, cervical lymphadenopathy, rashes, arthritis and gastrointestinal symptoms associated with synovial or serosal inflammation. HIDS is caused by mutations in the gene encoding mevalonate kinase enzyme. The febrile attacks usually start in early childhood and triggered by stress or vaccinations. We report a case of 16-month-old boy who had episodes of recurrent fever accompanied by maculopapular rash and lymphadenopathy. He was diagnosed as HIDS and he had heterozygote mutation of mevalonate kinase gene.

definite diagnosis was not done. He was treated with colchicine for 3 months by another paediatric rheumatology centre in our country, but did not have any clinical response. He was product of non-consanguineous parents with no known diseases. His developmental stages were delayed. His height and weight were less than third centile. On physical examination, he was febrile and appeared generally well. He had a fixed, tendered palpable mass of 3×3 cm diameter on the right submandibular region. Physical examination also showed diffuse erythematous lesions on the submandibular region, on the trunk, arms and he also had swelling, tenderness in his right knee with erythema (figures 1 and 2). The rest of physical examination was normal.

BACKGROUND

Hyperimmunoglobulinemia D syndrome (HIDS) is a rare, chronic autoinflammatory disease that belongs to periodic fever syndromes. HIDS was initially described by van der Meer in Dutch patients.¹ It is an extremely rare disorder; there are only few case reports from all over the world. Most of the patients with HIDS are reported from Holland and France.² It is an autosomal recessive syndrome caused by mutations in the mevalonate kinase (MVK) enzyme, which is involved in cholesterol synthesis pathway. HIDS presents with intermittent episodes of fever, lymphadenopathy, abdominal pain and rash. HIDS should be kept in mind in the differential diagnosis of infants and young children having attacks of recurrent fever with unknown origin. There have been five case reports from Turkey before.³ The patients were aged between 20 month and 17 years. The median age of onset of symptoms of the patient was 5 years. They had clinical findings similar to the present case; but to the best of our knowledge, our patient is the youngest one reported from our country.

CASE PRESENTATION

A 16-month-old boy was admitted with fever, maculopapular rash and cervical lymphadenopathy. He had a history of recurrent febrile episodes, since 4 months of age, the first attack being after the second dosage of diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccination.

The febrile attacks (up to 41°C) typically occurred in every 4–5 weeks, lasting for 4–6 days, accompanied by rash, aphthous ulcers, cervical lymphadenopathy and abdominal pain. He was well between episodes. He was evaluated several times but a

INVESTIGATIONS

A complete blood count showed a total leucocyte count of 26 100/mm³, haemoglobin of 8.7 g/dL and a platelet count of 689.000/mm³. Erythrocyte sedimentation rate was 73 mm/h, the C reactive protein level was 6.5 mg/dL. Laboratory analysis of the electrolyte, liver and renal function tests were all in normal ranges. Serum immunoglobulin levels were normal. Blood and urine culture did not yield any microorganisms. Peripheral smear, bone marrow study and chest radiography were normal. The viral serology, Brucella, Salmonella, Leptospirosis and Tuberculosis analysis were all negative. Tandem mass spectrometry was normal; urine organic acid analysis showed mevalonic aciduria (MA). The urinary mevalonic acid excretion was increased. Immunological testing including especially immunodeficiency, including serum immunoglobulin levels, peripheral blood lymphocyte subsets and nitroblue tetrazolium test were in normal limits. Rheumatoid factor, antinuclear antibody and anti-double-stranded DNA were all in normal limits. Serum IgD level was normal (18.3 IU/mL) during the attack-free period. Molecular testing of the patient confirmed the diagnosis of HIDS with D170D and c.769–38C>T(r35191208) heterozygote mutation.

DIFFERENTIAL DIAGNOSIS

HIDS has a wide spectrum of differential diagnosis including other periodic fever syndromes, mainly PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) and familial Mediterranean fever (FMF). PFAPA is characterised by especially cervical lymphadenopathy, but all lymph nodes

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Figure 1 Erythematous lesions of the patient.

may be affected in HIDS and attacks of severe abdominal pain is the main feature of FMF.

Infectious diseases and malignancies also should be ruled out because of a history of prolonged fever in patients with HIDS.

TREATMENT

The patient was given low-dose steroid (5 mg/day) and interleukin 1 (IL-1) receptor antagonist treatment (anakinra).

OUTCOME AND FOLLOW-UP

He had a dramatic clinical response to steroid and IL-1 receptor antagonist treatment; 1 week later he had relief of symptoms; lymphadenopathy and rash disappeared and infection markers were in normal ranges. He is still followed by our paediatric rheumatology department and he is asymptomatic on anti-IL-1 therapy.

DISCUSSION

HIDS is a rare autoinflammatory disorder that belongs to the family of hereditary periodic fevers. The common feature of hereditary periodic syndromes is cytokine-mediated autoinflammation associated with a self-limiting febrile attack. The febrile attacks typically start in infancy with a median age of 6 months. The fever episodes are characterised by rapid onset of fever, often above 40°C, accompanied by shaking chills. The attacks typically last 3–6 days, recurring every 4–8 weeks and the fever stays high until the end of episode. The intervals between attacks can vary from one patient to another and are prolonged as the patients become older. The attacks can be evoked by emotional stress, minor trauma, infections or vaccinations, as in the first attack of our patient.⁴ The most frequent symptoms that accompany episodes are lymphadenopathy, skin lesions, aphthous ulcers, arthralgia, arthritis and gastrointestinal findings.⁵ The lymphadenopathy is usually painful and primarily in the cervical region like our patient, but sometimes can be generalised and accompanied by splenomegaly. The skin lesions of HIDS are usually erythematous maculopapular rashes, urticarial and aphthous ulcers mimicking Behçet's disease.⁶ The gastrointestinal manifestations are vomiting, diarrhoea and abdominal pain associated with serosal inflammation. The abdominal pain can be so severe and resemble acute abdomen as patients with

Figure 2 Erythematous lesions of the patient.

FMF. Another symptom of HIDS is arthralgia or arthritis. It is usually symmetrical, polyarticular, non-destructive and usually involves large joints, as in our case.

The HIDS is caused by mutations in the MVK gene on the long arm of chromosome 12. More than 63 mutations have been reported in the MVK gene, the most common mutation is V377I. MVK deficiency leads to two different clinical entities having severe and mild ends. The homozygote mutation results in MA, in which the enzyme activity severely reduced (<0.5%). MA phenotype presents with psychomotor retardation, microcephaly, hypotonia, ataxia and cerebellar atrophy. The patients with MA also have recurrent febrile episodes. The enzyme activity is 1–20% in HIDS.⁷

MVK is an essential peroxisomal enzyme in the pathway of isoprenoid and cholesterol biosynthesis. There is no proven pathophysiology of HIDS, but decrease of isoprenoids results in the production of IL-1 β that triggers inflammation. The plasma levels of IL-6, IL-1 and tumour necrosis factor α (TNF- α) have been shown to increase during inflammatory attacks of HIDS. The activation of cytokines suggests the use of anticytokines in the treatment of HIDS.⁸ Anti-TNF- α agents (etanercept), IL-1 receptor antagonists (anakinra, canakinumab) and anti-IL-6 receptor therapy have been successfully used in patients with HIDS.^{9,10} Colchicine is not effective in the treatment of HIDS, as in our case who used it for 3 months. Even then, it is suggested that unresponsiveness of colchicine can be used in the

differential diagnosis of HIDS. The usage of steroids has also been reported to decrease the severity of attacks. Moreover, haematopoietic stem cell transplantation can be effective in severe MVK deficiency.¹¹

We began the treatment of our patient both with steroid and anakinra to have a rapid response, because of prolonged history and severity of attacks. We plan to continue our treatment only with anti-IL-1 therapy.

The elevated levels of serum IgD are not observed in all of the patients with HIDS and are not necessary for the diagnosis. In a multicentre study, 22% of patients with HIDS had normal IgD levels.¹² It is reported that IgD levels tended to rise as patients grew older. Moreover, serum IgA can be elevated in patients with HIDS. Indeed our case had normal levels of IgD and IgA.

Although, HIDS was previously reported as a mild disorder, the AA type amyloidosis is reported in patients with HIDS like other autoinflammatory disorders.¹³

In conclusion, HIDS is not a benign disease as suggested before. It begins in the early period of life and has a negative effect on the life quality of the patient. The most important clue

for diagnosis is to suspect about the disease. HIDS should be kept in mind for patients having a history of recurrent fever of unknown origin.

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Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Although most of the patients with HIDS are from Dutch ancestry, HIDS can be seen all over the world.
- ▶ We must remember HIDS in the differential diagnosis of infants and young children with recurrent fever of unknown origin, especially if the fever is accompanied by rash and cervical lymphadenopathy.
- ▶ The first attack of HIDS is usually reported after the first dosage of childhood vaccination, so HIDS should also be remembered if an infant presents with typical clinical symptoms after vaccination.
- ▶ Early diagnosis will increase the quality of life of patients with HIDS and improve the prognosis.

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