Mevalonate kinase deficiency (hyper IgD syndrome with periodic fever) - different faces with separate treatments: two cases and review of the literature

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The hyperimmunoglobulinemia D syndrome (HIDS), so-called mevalonate kinase deficiency, is caused by recessive mutations in the gene encoding mevalonate kinase enzyme. HIDS is characterized by recurrent fever attacks of 3-7 days that begin in infancy and recur every 4-6 weeks. The febrile period is accompanied by lymphadenopathy, arthralgia, abdominal pain, diarrhea, aphthous ulcers, and varying degree of skin involvement. The course and severity of the disease may be quite different. There is no effective or proven therapy for HIDS. We report two cases with HIDS, which had separate clinical findings and treatment strategies.

Key words: hyperimmunoglobulinemia D syndrome, mevalonate kinase deficiency.

The hyperimmunoglobulinemia D syndrome (HIDS) is caused by recessive mutations in the gene encoding mevalonate kinase enzyme (MVK). This enzyme has a role in the pathway of cholesterol and nonsterol isoprenoid biosynthesis[1]. MVK gene mutations may cause reduced activity of the enzyme resulting in HIDS or a complete deficiency of the enzyme resulting in mevalonic aciduria (MVA) with neurological symptoms. The pathogenesis is unclear. The association between the defective isoprenoid biosynthesis and inflammation is still poorly understood. Monocytes and macrophages produce higher levels of tumor necrosis factor alpha (TNF-α), interleukin 1beta (IL-Iβ) and interleukin 6 (IL-6) during the febrile attacks[2,3]. HIDS is characterized by recurrent fever attacks of 3–7 days that begin in infancy and recur every 4–6 weeks. The febrile period is accompanied by lymphadenopathy, arthralgia, abdominal pain, diarrhea, aphthous ulcers, and skin involvement of varying degree. There is no symptom between the attacks. During the attacks, acute-phase reactants, especially C-reactive protein (CRP), increase[4,5]. The clinical association of febrile episodes with high serum immunoglobulin D (IgD) levels and detection of MVK enzyme defect are required for the diagnosis. There is no effective or proven therapy for HIDS. Commonly used anti-inflammatory drugs (colchicine, steroids) have little effect on suppressing the attacks. There are some randomized trials with simvastatin, thalidomide, anakinra, and etanercept[6]. This paper presents two HIDS patients with different clinical findings and treatment strategies.

Case Reports

Case 1

An 11-year-old girl was admitted with a history of recurrent fever, abdominal pain, arthritis of the fingers, cervical lymphadenopathy, weakness, fatigue, and headaches. The attacks started at the age of 15 months. Each attack lasted for about one week, 2-3 times annually. She was given antibiotics each time with a presumed diagnosis of upper airway infection. On one of the occasions, laboratory tests revealed an elevated erythrocyte sedimentation rate (ESR) of 102 mm/h (0-20 mm/h) and CRP level of 175 mg/L (<0.5 mg/L). Her parents were non-consanguineous and the

family history was unremarkable.

On admission, she was growing well with a height at the 75th and weight at the 50th percentile. She had arthritis of the fourth proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints on the right hand. Examinations of the joints and systems were unremarkable. Laboratory investigations showed a moderate decrease in hemoglobin (10.2 g/dl) consistent with chronic disease anemia and a normal platelet count (244,000 /mm3) and white blood cell count (9100 / mm^3). Urine analysis and C3 and C4 levels were normal. The plasma Ig levels were elevated: IgA 476 mg/dl (57–282 mg/dl); IgG 2,550 mg/dl (480–1,240 mg/dl); IgM 433 mg/dl (78–261 mg/dl); and IgE 523 mg/dl (<99 mg/dl). Regarding the frequency of familial Mediterranean fever in our community, mutation analysis of the MEFV gene was done and found as negative for the 12 common mutations screened. HIDS was the second presumed diagnosis because of recurrent prominent cervical lymphadenopathies with headaches. The plasma IgD level was found to be elevated, at 228 mg/dl (0-80 mg/dl). Mutation analysis of the mevalonate kinase gene was performed in the Gaslini Institute, Italy. The patient was found to have two mutations: V377I on exon 11 (c.1129G>A, GTC(valine) →ATC(isoleucine)), and c.38_39 ins TCTG frameshift on exon 2 (p.K13NfsX66). On follow-up, she had two mild attacks in the last year; one of them was treated with single high-dose oral prednisone.

Case 2

A 2.5-year-old boy presented with a history of recurrent fever, abdominal pain, bloody diarrhea, and cervical lymphadenopathy. His medical history revealed similar attacks repeating every month from the age of two months. Family history included an uncle with chronic renal failure of unknown cause. His parents were non-consanguineous. He was first admitted to the hospital at the age of five months. He had a temperature of 39°C and bloody diarrhea resembling a bacterial gastroenteritis. The high fever subsided in four days following parenteral ceftriaxone, despite no available growth in blood and stool cultures.

On admission, at the age of 2.5 years, the physical examination was unremarkable, except for splenomegaly. Laboratory examination revealed a hemoglobin level of 7.8 g/dl, hematocrit 24%, white blood cell count 12,100/ mm^3, and platelets 454,000/mm^3, with marked increases in ESR as 73 mm/h (0-20 mm/h) and CRP as 191 mg/L (0-8 mg/L). The blood and urine cultures were negative. He had a combined anemia with chronic disease and iron deficiency. Brucella, Salmonella, Epstein-Barr virus (EBV), TORCH, and human immunodeficiency virus (HIV) serologies were negative. A bone marrow aspiration excluded malignancy, hemophagocytosis and storage diseases, and was compatible with infection and inflammation. The plasma immunoglobulin and complement levels were normal except IgG, and antinuclear antibodies (ANA) and anti-dsDNA were negative. No pathogen organism was isolated from blood and urine cultures. He was given broad-spectrum parenteral antibiotics. The fever resolved on the fifth day.

Due to the recurrence of febrile attacks, the family history and common frequency of familial Mediterranean fever in Turkey, MEFV mutation was done and he was found heterozygous for V726A; however, there was no response to six months of colchicine treatment. Considering the age and clinical findings, HIDS was the other presumed diagnosis, despite normal levels of IgD, which can be found as normal under the age of five. Unfortunately, we could not evaluate the urine mevalonic acid levels of these two patients between attacks because the test is not available in our laboratory. Mutation analysis of the mevalonate kinase gene was performed in the Gaslini Institute, Italy. He had two mutations: one was I268T on exon 8 (c.803T>C ATA (isoleucine) →ACA(threonine)), and the other was V377I on exon 10 (c.1129G>A GTC(valine) →ATC(isoleucine)). The treatment was switched to simvastatin, which inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway. He experienced less frequent but still severe attacks, which could be controlled with additional steroids. Regarding the therapeutic role of biologics, etanercept, a soluble TNF-α receptor blocker, was started. It was switched to anakinra, an IL-1 inhibitor, six months after the initiation of etanercept, which was deemed not useful. Control of the attacks was

successful after anakinra; however, the patient could not tolerate the daily painful injections. The disease is still uncontrollable without additional steroids.

Discussion

Hyperimmunoglobulinemia D syndrome (HIDS), or mevalonate kinase deficiency, is due to mutations of the gene coding for mevalonate kinase enzyme. The syndrome is inherited as an autosomal recessive trait, and half of the patients with this syndrome have affected siblings[1,3].

Human MVK is located on chromosome 12q24, and almost 63 pathological sequence variations have been reported throughout its 10 coding exons[7]. The four most common mutations, V377I, I268T, H20P/N, and P167L, account for more than 70% of the total found. There is no clear relationship between severity of disease, onset of symptoms, number of attacks per year, and a specific mutation within the milder HIDS phenotype[8]. Patients carrying homozygous V377I mutation have mevalonic aciduria due to lower MVK enzyme activity[4]. As in the previous study, Mandey et al.[7] showed that the mevalonate kinase levels decreased in patients who carried the compound heterozygous mutation I268T/V377I and homozygous mutation I268T/I268T in their 57-patient cohort. This is likely why the second patient, carrying I268T/V377I compound heterozygous mutation, had more severe, drug-resistant attacks and also had heterozygous mutation (V726A) of MEFV. The first patient, on the other hand, had milder clinical features.

Ayaz et al.[13] showed that having the additional MEFV mutation increased the clinic severity in a cohort of patients with systemic onset juvenile idiopathic arthritis (SoJIA). Yalçınkaya et al.[14] demonstrated that having the MEFV mutation was a predisposing factor for childhood polyarteritis nodosa (PAN). In light of the related papers, the more severe and drug-resistant clinic of the second patient might be due to having the additional heterozygous MEFV mutation.

As in our patients, the most frequent clinical finding is recurrent attacks of fever, usually starting in infancy. Gastrointestinal symptoms such as severe abdominal pain mimicking acute abdomen and diarrhea are major symptoms of the disease. Lymphadenopathy during the attacks is very common and is found in 94% of the patients, and splenomegaly during febrile episodes is reported in 48% of patients, mainly in children[6]. The wide variety of the clinical spectrum of HIDS in the patients above seems to correlate with the type of genetic mutations. In the first patient, the attacks were infrequent, and symptoms were not severe and did not require aggressive treatment. However, the second patient had weekly severe and drug-resistant attacks.

In HIDS patients, elevated levels of IgD may provide a clue to the diagnosis, but it is not diagnostic. Although the majority of patients have an elevated IgD, 22% had normal levels, such as seen in our second patient. Moreover, Medlej-Hashim et al.[9] showed that elevated serum IgD levels have also been described in other auto-inflammatory diseases, though they did not correlate with symptoms. A recent study by Ammouri et al.[10] found the negative predictive value of a normal IgD level in mevalonate kinase deficiency to be as low as 58%.

Various therapeutic approaches have been undertaken to suppress inflammation, such as methotrexate, azathioprine, sulfasalazine, tacrolimus, dapsone, intravenous immunoglobulins, montelukast, anakinra, and etanercept; however, there is no consensus on the treatment of HIDS. Prednisone can reduce the severity and duration of attacks if it is given in the early phase.

The prognosis of HIDS also varies as do its clinical features. Frequency of the attacks usually diminishes as the child gets older. Complications such as recurrent peritonitis resulting in abdominal adhesions and joint contractures as a result of arthritis are rare. Amyloidosis, resulting in renal failure, is also a quite rare complication of HIDS[11]. In 2004, Obici et al.[12] from Italy published the first patient (a 27-year-old male) with amyloidosis associated with HIDS. Our first patient continues to have rare and mild attacks without any complications, and she is presumed to have a normal life. On the other hand, the second patient with weekly drug-resistant attacks is at risk for peritoneal adhesions and, albeit rare, amyloidosis.

Although familial Mediterranean fever is the most common auto-inflammatory disease in Turkey, other auto-inflammatory diseases like HIDS should be kept in mind, especially when the attacks are prolonged and resistant to colchicine. Mutation analysis is mandatory to confirm the diagnosis, since the clinical features could be quite different and IgD levels are not diagnostic.

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