Hyperimmunoglobulin-D Syndrome in Children: A Review Article

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Abstract

Hyperimmunoglobulin-D syndrome (HIDS) is a rare, autosomal recessively inherited autoinflammatory disease caused by mutations in the mevalonate kinase gene. HIDS usually starts in infancy with recurrent fever episodes lasting three to seven days and recurring every three to six weeks, with only partial symptom decrease in adulthood. Fever is typically accompanied by abdominal pain, vomiting, diarrhea and cervical lymphadenopathy, and sometimes by skin and joint symptoms. Blood leukocytes and serum C-reactive protein (CRP) are elevated during the episode, and in addition, high levels of interleukine-1 (IL-1), IL-6 and tumor necrosis factor (TNF) and respective soluble receptors are measured. Currently, there is no established treatment for HIDS. So far, four children have been successfully treated by TNF-alpha inhibitor (etanercept) and three children with IL-1 receptor antagonist (anakinra). The current study is a narrative review about the updates of HIDS.

Keywords: Hyper IgD Syndrome, Mevalonate Kinase Deficiency, Child

1. Context

Hyperimmunoglobulin-D syndrome (HIDS) was initially described in 1984 by Jos van der Meer (1). The hereditary periodic fever syndromes are a group of monogenetic disorders that present with recurrent bouts of fever and its associated manifestations (2, 3). Deficiency of mevalonate kinase (MVK) is associated with two rare periodic fever syndromes, a severe form, mevalonic aciduria (MA) and a milder form, HIDS (4). Hyperimmunoglobulin-D syndrome (HIDS) also known as mevalonate kinase deficiency (OMIM # 260920) is a rare and autosomal recessively inherited autoinflammatory syndrome caused by mutations in the MVK gene (5). The classical form of HIDS due to partial MVK deficiency occurs in about 75% of the known cases.

The typical clinical picture of HIDS consists of recurrent fever episodes accompanied by cervical lymphadenopathy, abdominal pain, vomiting, and diarrhea along with joints and skin symptoms. The attacks usually start during the first year of life, last three to seven days and recur every three to six weeks, with partial improvement in adulthood. Serum C-reactive protein (CRP) is high during the acute attack. Instead, serum immunoglobulin D (IgD) is usually normal until the age of three. Elevated levels of interleukine-1 (IL-1), IL-6 and tumor necrosis factor (TNF) and corresponding soluble receptors are found during the attacks. The patients are free of symptoms between the attacks (2). Before the occurrence of attacks, there may be a triggering response like vaccination (6).

2. Evidence Acquisition

To update about HIDS, PubMed and Google Scholar database were searched for terms hyper IgD syndrome, and children alone and in combinations and limited to the articles published in English-language journals. The qualitative results are presented here.

3. Results

3.1. Etiology and Pathology

MVK gene is located on the long arm of chromosome 12 (12q24) that encodes mevalonate kinase (MK) (4). 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 (2). The mechanisms by which abnormalities in MVK activity cause febrile episodes are unclear. Mevalonate kinase (a homodimeric enzyme) is a key enzyme in the cholesterol metabolic pathway and follows 3-hydroxy- 3-methylglutaryl-coenzyme a reductase (Figure 1).

In patients with the hyper-IgD syndrome, the activity of mevalonate kinase is reduced 5% - 15% of normal; as a result, serum cholesterol levels are slightly reduced, and during attacks, urinary excretion of mevalonic acid is slightly elevated. Most patients are compound heterozygotes for missense mutations in

the gene for mevalonate kinase. The two most common mutations are c.1129G > A (rs28934897) a residue 377 (V377I) a variant that is the substitution of isoleucine for valine, is present in more than 80% of patients (52% - 90%) and the substitution of threonine for isoleucine at residue 268 (I268T) (7).

Cuisset et al. found that it is the cause of a severe form of hyper-IgD/mevalonate kinase deficiency. The mutation p.R277G lowers the binding affinity for the substrates of some enzymes. Interestingly, they found that p.R277G mutation inhibits binding of isopentenyl pyrophosphate (IPP) (binding free energy = 0 kcal/M), one of the isoprenoids responsible for feedback-inhibition of MVK (8).

The V377I mutation results in a slight reduction of the stability of recombinant human mevalonate kinase protein and in the catalytic activity of the enzyme. Less than 1% of patients have a complete deficiency of mevalonate kinase, associated with mevalonic aciduria, a rare inherited disorder characterized by developmental delay, failure to thrive, hypotonia, ataxia, myopathy and cataracts. In mevalonic aciduria, the disease-associated mutations are mainly clustered within a specific region of the protein. How a deficiency of mevalonate kinase is linked to an inflammatory periodic fever syndrome is not yet known (9). Additionally, patients with a combination of mutations in two HPF genes (e.g., in the MEFV and TNFRSF1A-gene) are reported, which can modify the phenotype (10, 11). Some studies showed that innate immune cells such as macrophages, neutrophils, and monocytes are involved (12). Circulating lymphocytes from patients with HIDS with periodic fever syndrome have decreased apoptosis.

3.2. Epidemiology

Most of the initially reported cases of HIDS were from Europe; other cases from Turkey, Armenia, United States and Japan were reported too (12).

A case of HIDS is reported in an Arab child (13). Half of the patients with HIDS registered in the international database (http://www.hids.net) are from the Netherlands. One patient is registered from Finland, and no other patients are registered or reported from Scandinavian countries (2). It is the most prevalent periodic fever syndrome, affecting more than 10,000 patients worldwide. However, HIDS is more common in the Netherlands, France, Germany and western Europe (3). The male-to-female ratio was equal in one study but about 3:2 in another large series (8, 14).

3.3. Clinical Features

Typically, patients with HIDS have recurrent attacks of fever that start during the first six months of life. Fever continues three to seven days, typically less than seven days, and can be provoked by vaccinations, minor trauma, infections, other physical or emotional stress and surgery, although the triggers for most attacks are unknown. Attack manifestations are shown in Box 1. Cervical lymphadenopathy and abdominal pain with vomiting, nausea and diarrhea often accompany the attack. Joints, skin and mucous membrane symptoms are often present. The patients are free of symptoms between the attacks, and the children grow and develop normally. The typical features of HIDS are described in Box 2. Most patients have prodromal symptoms that include nasal congestion, sore throat, backache, fatigue, vertigo, headache and even behavioural changes. HIDS generally have regular patterns. They have a normal life span. Generally, the attacks recur every four to six weeks, but the intervals may vary in a patient and especially between different patients. Patients with HIDS suffer from febrile attacks throughout their lives; though, the attack rate is the highest in childhood. Unlike familial Mediterranean fever (FMF) and TNF receptor associated periodic syndrome (TRAPS), amyloidosis is quite low (15). The attacks persist throughout life, although patients have a reduction in intensity and frequencies of attacks after adolescence. Therefore, the symptoms tend to become less prominent in adults. Chronic complications in adulthood were rather rare in 103 patients followed-up until 16.5 - 57.5 year old: amyloidosis in three, abdominal adhesions in 10 and joint contractures in four cases with no HIDS-related mortality. The 10% occurrence of abdominal adhesions suggests that abdominal pains during acute attacks are most probably caused by sterile peritonitis. The disease onset took place in all cases during childhood, the median age being six months. Vaccinations precipitate attacks in 54% of patients.

In some times, there is more than one mutation in different genes of monogenic autoinflammatory diseases in the same individual. Therefore, atypical clinical manifestations such as the overlap features of both FMF and HIDS are reported (16).

Amyloidosis is not reported in any of the patients with this syndrome.

3.4. Laboratory Findings

All patients had a vigorous acute-phase response during attacks, with elevated ESR (median, 76 mm/h), leukocytosis (median, 15,000 per mm^3), and C-reactive protein (median, 163; range, 36 to 404 mg/L). Between attacks, some patients had continuous elevation of inflammation markers, although much lower than the ones during attacks. An elevation of serum polyclonal IgD is considered a hallmark of the disease. The median IgD concentration of the highest IgD measured in the patients was 400 mg/dL (range, 8 to 5300 mg/dL). However, an elevated IgD concentration was not universally present in HIDS patients: in 22% of the patients, the highest measured concentration of IgD was below the upper limit of normal (100 mg/dL). Elevation of serum IgD is frequently accompanied by elevation of serum IgA. A high level of IgD and IgA accompanies these symptoms and is often used as a diagnostic confirmation of HIDS (17).

Data about serum IgA concentration was available for 86 patients. In 55 patients (64%), the IgA concentration was above the upper limit of normal, 260 mg/dL (median, 405 mg/dL) (18). Serum cholesterol level is usually low to normal. The most common differential diagnosis of HIDS is mevalon-

ic aciduria (MVA) characterized by psychomotor retardation, ataxia, failure to thrive, cataracts, and dysmorphic features.

3.5. Diagnosis

The diagnosis of HIDS may be confirmed by the presence of two mutations in MVK and/or elevated mevalonate in urine during acute attacks. Elevation of serum IgD level is not universally present, especially in young children. Elevation in serum IgD level may be present in autoinflammatory diseases as well as some chronic infections.

Urinary mevalonic acid/creatinine ratio (> 20 mM/M creatinine) is suggestive of HIDS (19).

Basically, diagnosis of MK deficiency relies first on biochemical tests revealing the enzymatic defect (the presence of mevalonate in urine (during fever episodes in HIDS) and/or decrease in the mevalonate kinase activity during the asymptomatic interval) and second, on confirmation by DNA sequence analysis (20, 21).

An accurate clinical history and a physical examination remain the first diagnostic tools. HIDS can be diagnosed by typical clinical characteristics and continuously high serum IgD values (> 100 mg/dL) on two occasions at least fist month apart. However, serum IgD may be low in children younger than three years as also observed in the first Finnish patient. Over 80% of the patients have elevated IgA levels, usually increasing in conjunction with the increase of IgD by age. During an acute attack, there is a prominent acute phase reaction with leukocytosis in blood and high CRP and amyloid A (SAA) in serum, but serum procalcitonin may be normal or only moderately elevated. Erythrocyte sedimentation rate increases. However, serum ferritin does not reach such high concentrations as found in the Still disease. Many pro-inflammatory and inflammatory cytokines, particularly IL-1, IL-6 and TNF-alpha and their soluble receptors increase during the attacks. Urinary mevalonic acid modestly increases during the acute attack, whereas the values in patients with MVA are much higher. Likewise, cellular mevalonic acid concentrations may increase in patients with HIDS reflecting the reduced activity of the MVK enzyme (2).

3.6. Treatment

Currently, there is no established treatment for HIDS, and the available experience comes from individual case reports. Colchicine used in FMF and immunoglobulins used in many inflammatory diseases, as well as cytotoxic drugs used in malignant and severe rheumatic diseases, were mainly ineffective. Very few patients respond to Colchicine. Recently, the combination of prednisolone, azathioprine and intravenous immunoglobulins resulted in reduced incidence and severity of febrile attacks in six- and eight-year-old brothers with HIDS caused by typical compound V377I and I126T mutations associated with hypogammaglobulinemia caused by B-cell cytopenia. Thalidomide was studied in a randomized controlled trial in adults, and the result was negative. Systemic steroids and statins, mainly simvastatin, were partially effective in adults. Etanercept, TNF-alpha inhibitor, anakinra and IL-1 receptor antagonist are reasonable alternatives in the treatment of HIDS, since TNF-alpha and IL-1 seem to play a central role in acute HIDS attacks. Infliximab, a humanized monoclonal antibody against TNF-alpha, and tocilizumab, a humanized monoclonal antibody against IL-6, might be also possible alternatives (22).

One patient with severe keratopathy associated with HIDS was successfully treated with infliximab, but there are no published reports on tocilizumab in HIDS. In the long-term follow-up, a third of the adult patients had benefited from steroids, and 9% were successfully treated with etanercept, 7% with anakinra and 6% with statins. Either etanercept or anakinra relieved the symptoms in 80% of the ones who received these drugs (23, 24).

Kostjukovits et al. treated 21 patients with HIDS with anakinra and another 16 with etanercept, resulting in complete or partial responses in 90% and 50% of the cases, respectively. A further five patients were treated with canakinumab, with complete or partial responses (25).

The major disadvantage of anakinra is the occurrence of painful injection site reactions.

Four children were successfully treated with etanercept and two children with anakinra. In addition, anakinra had a dramatic effect in a 20-year-old male who had experienced periodic fevers since he was two years and renal failure leading to renal transplantation at the age of 10 (2). Milder disease may respond to non-steroidal anti-inflammatory drugs. A report showed that Simvastatin, (HMG-CoA reductase inhibitor) may be useful to treat inflammatory attacks in HIDS (26).

Canakinumab, 2 - 7 mg/kg every four to eight weeks, a long acting monoclonal antibody directed against IL-1β is effective in reducing both frequency and severity in patients with mild and severe MKD in case reports and observational case series (27, 28).

Tocilizumab was described by Stoffels et al. who also observed reduction of frequency and severity of the inflammatory attacks, although after several months of treatment one of these two patients persistently showed mild inflammatory symptoms in the absence of biochemical inflammatory markers (29).

A beneficial effect of human monoclonal anti-TNFα antibody adalimumab was observed in a small number of MKD patients, where the two patients in the Euro fever registry, treated with adalimumab, showed only partial or no response (30).

Several case reports, including one in the past two years, describe a beneficial effect of hematopoietic stem cell transplantation on the neurologic and inflammatory symptoms in severe mevalonate kinase deficiency (31, 32).

3.7. Prognosis

Patients have a good prognosis because amyloidosis is not reported in HIDS. There are no apparent neurologic or morphologic abnormalities. Patients with HIDS typically have a normal life expectancy (5, 33).
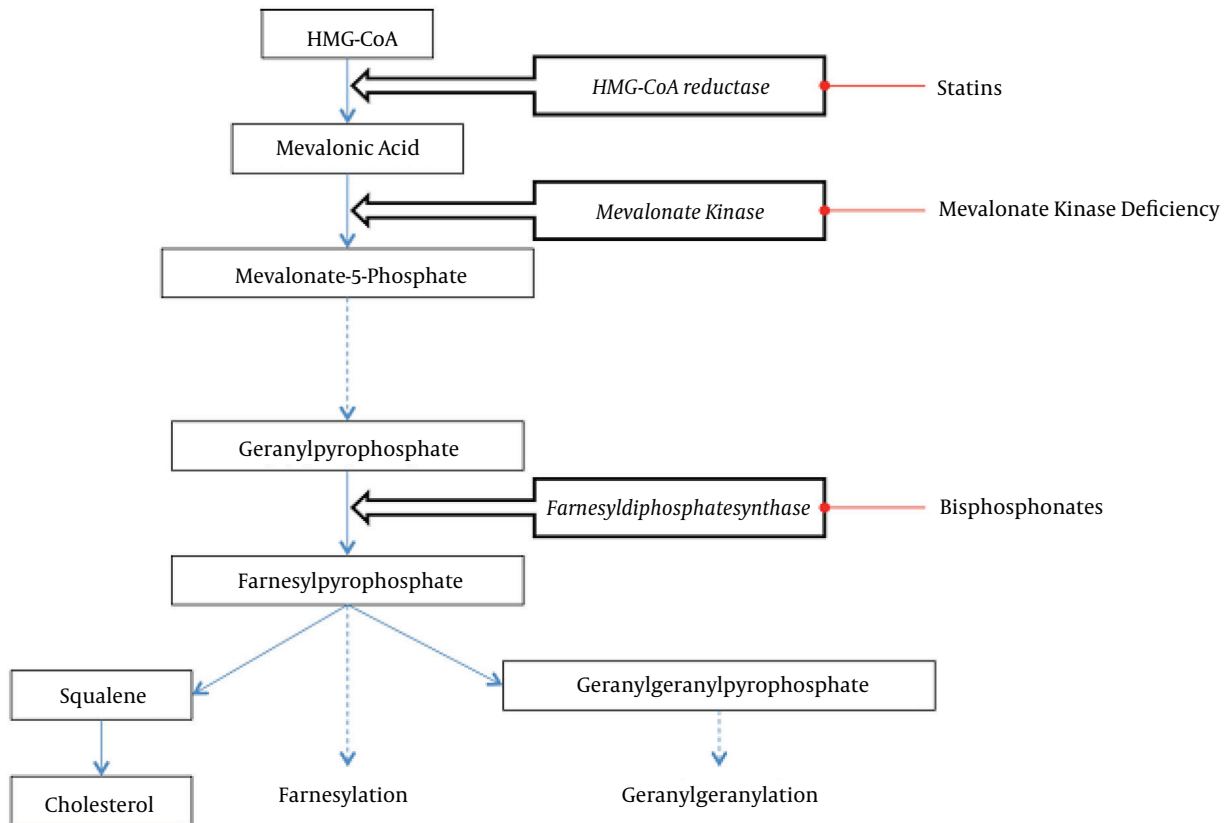
Figure 1. Mevalonate Kinase Catalyzes the Phosphorylation of Mevalonic Acid

Box 1. Attack Manifestations in HIDS

Attack Manifestations
About 94% of patients have lymphadenopathy. (Tender and/or rubbery on palpation) and biopsy shows hyperplasia and the presence of plasma cells.
High, spiking fever is preceded by chills in 76% of patients
72% of patients reported abdominal pain
56% reported vomiting
82% reported diarrhea
52% reported headache
Polyarthralgia reported in 80%
A non- destructive arthritis and/or arthralgia was reported in 68% of the patients (mainly of the large joints e g, knee and ankle)
About 82% of the patients reported skin lesions (erythematous macules and papules and sometimes petechia and purpura)
Serositis was observed in only a minority of the patients
Aphthous ulcers in the mouth or vagina
Splenomegaly

Abbreviation: HIDS, hyperimmunoglobulin-D syndrome.

Box 2. Characteristics of Patients With HIDS and Periodic Fever

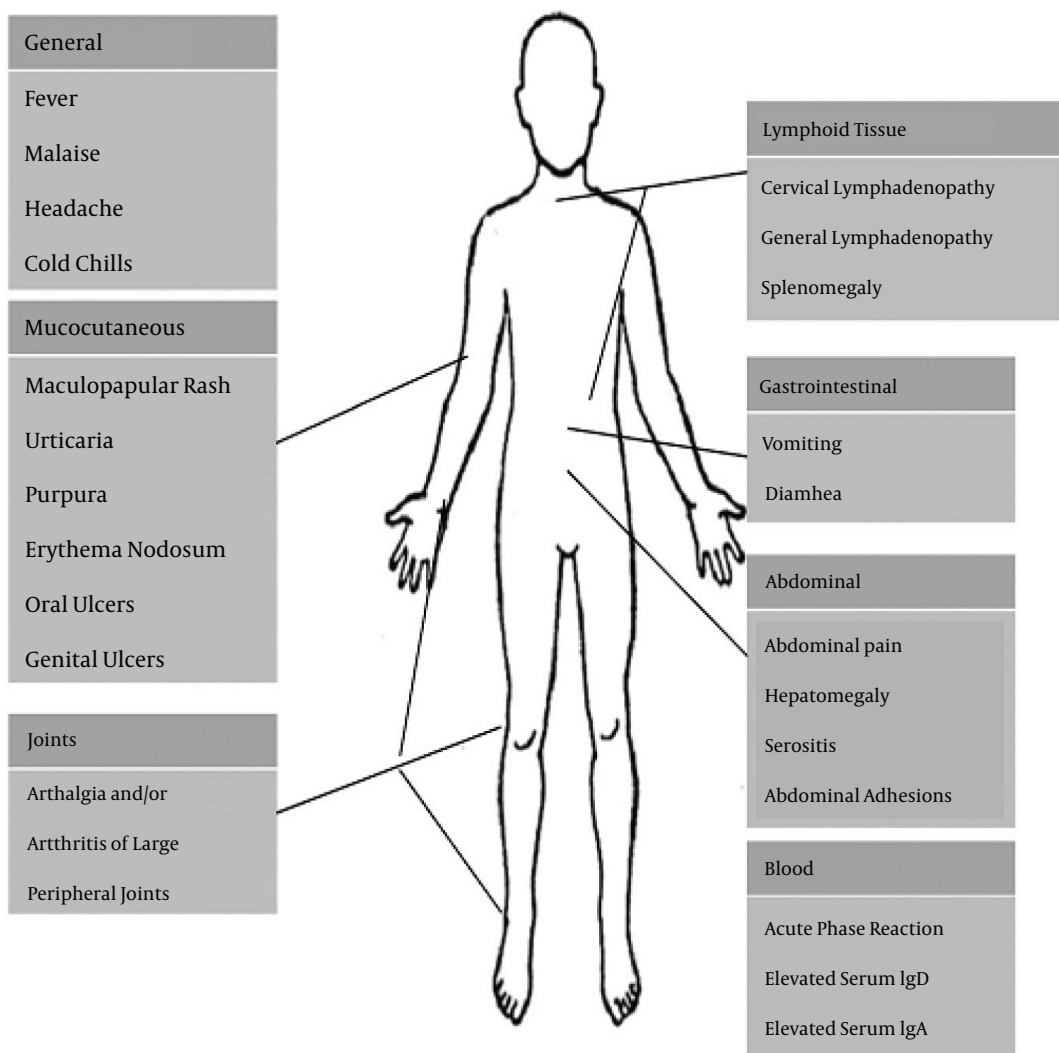| Characteristics of Patients |
| --- |
| Early onset at <12 months |
| Fever episodes every four to six weeks |
| Duration of fever episodes four to seven days |
| Marked response in acute phase reactants |
| Abdominal pains, nausea, vomiting and diarrhea often present |
| Cervical lymphadenopathy |
| Occasionally splenomegaly |
| Diffuse macular rash, aphthous ulcer, headaches |
| Arthritis and or arthralgia (oligo or polyarticular patterns) |
| No response to antibiotics |
| No or partial response to systemic steroids |
| Partial spontaneous resolution by age (1) |

Abbreviation: HIDS, hyperimmunoglobulin-D syndrome.

General
Fever
Malaise
Headache
Cold Chills

Mucocutaneous
Maculopapular Rash
Urticaria
Purpura
Erythema Nodosum
Oral Ulcers
Genital Ulcers

Joints
Arthalgia and/or
Artthritis of Large
Peripheral Joints

Lymphoid Tissue
Cervical Lymphadenopathy
General Lymphadenopathy
Splenomegaly

Gastrointestinal
Vomiting
Diamhea

Abdominal
Abdominal pain
Hepatomegaly
Serositis
Abdominal Adhesions

Blood
Acute Phase Reaction
Elevated Serum lgD
Elevated Serum lgA

Figure 2. Clinical Manifestations in Hyperimmunoglobulin-D Syndrome

4. Conclusions

In conclusion, HIDS is a rare disease that starts early in life with lifelong recurrent attacks of fever accompanied by a variety of symptoms, including lymphadenopathy, abdominal pain, arthralgia, vomiting and diarrhea, skin lesions, and aphthous ulcers with a good prognosis. There is a gradual decrease in the number of attacks with increasing age. Prednisone, anakinra and etanercept can be effective in some patients to reduce the severity of attacks.

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