Chapter 2
Mevalonate Kinase Deficiency (MKD)/ Hyperimmunoglobulin D Syndrome (HIDS)

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Introduction

Mevalonate kinase deficiency (MKD)/hyperimmunoglobulin D syndrome (HIDS) is a rare autoinflammatory disease which was first discovered by Rowe and Fahey in 1965 [1]. Being an autosomal recessive disease, it is believed to result from a mutation in mevalonate kinase (MVK) gene – an enzyme involved in the phosphorylation of mevalonic acid, a component in the isoprenoid and cholesterol biosynthesis pathway [2]. Isoprenoids, including farnesyl, geranyl, and ubiquinone, are essential compounds in diverse cellular functions, and isoprenoid compounds affect the stability and maturation of MVK [3].

On the more severe end of the spectrum, mevalonic aciduria (MVA) usually occurs in childhood, during the first decade of life, and is often fatal, whereas HIDS manifestations are much milder and not life-threatening. There have been cases of adult onset HIDS described in literature. Observational study by Durel et al. [4] describes 23 patients with adult HIDS with mean age at diagnosis being 40 years. In this study significant amount of adult patients (65%) presented with abating severity and frequency of attacks with age, but only 35% were able to achieve remission.

Because of extreme rarity of the condition, with only close to 300 cases reported worldwide, very little has been published about incidence and prevalence of MKD and HIDS in particular. With the largest cohorts of patient registered in Northern Europe, some studies report prevalence of 5 cases of HIDS per 1,000,000 in the

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whole population in the Netherlands [5]. Highest prevalence of HIDS was observed in patients of Dutch and French descent.

The symptoms can be very nonspecific; hence, it becomes challenging to differentiate with other periodic fever syndromes. Wide spectrum of disease severity is defined by the severity of the enzymatic defect stemming from a variety of MVK gene mutations [6].

Increased levels of immunoglobulin D (IgD) as well as high levels of the cytokines, mainly IL 1, IL 6, and tumor necrosis factor-α (TNFα) are usually observed in majority of the patients.

Differential diagnoses include tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), juvenile systemic granulomatosis, juvenile idiopathic arthritis, familial Mediterranean fever (FMF), and Behçet disease.

Pathophysiology and Genetics

HIDS is considered a classic monogenic recessively inherited disease resulting from a defect in the gene encoding mevalonate kinase (MVK), an enzyme in which the end products include cholesterol, protein isoprenylates (including the prenylated Ras/Rho proteins), dolichol, and ubiquinone [7].

The most common mutation in MKD is p.V377I (G1129A); this mutation is observed primarily among heterozygous individuals with HIDS [8]. Less frequently observed mutations are I268T, H20PIN, and P167L, but their associations with the frequency or severity of febrile attacks have not been demonstrated (Table 2.1). One study found that the vast majority of V377I alleles from MKD patients who were geographically clustered in Western Europe shared a common ancestral origin [9]. The carrier frequency of any MVK mutation in the Dutch population is 1:65 [10]. Although MKD is a recessive disorder, it may also exhibit a pseudodominant pattern of inheritance; in one study, a mother and her two monozygotic twins had MKD [11].

The exact pathogenesis of HIDS still remains unclear. However, several of the isoprenoid end products have been involved in posttranslational events affecting lipid synthesis, protein degradation, and apoptosis [14]. A link between the isoprenoid pathway and apoptosis was also suggested by Nagashima et al. [15] who also showed that inhibition of this pathway by statins induced apoptosis in rheumatoid arthritis

Table 2.1 Most common MVK mutations

Most common MVK gene mutations from van der Hilst registry [12]	Most common MVK gene mutations from Eurofever registry [13]
V377I	p.V377I + p.V377I
I268T	p.V377I + p.I268T
H20P/N	p.V377I + p.G335A
P167L	p.V377I + p.G336S
H380R	p.V377I + p.L264F
R215Q	p.V377I + p.L265R
W188X	p.V377I + p.P165L

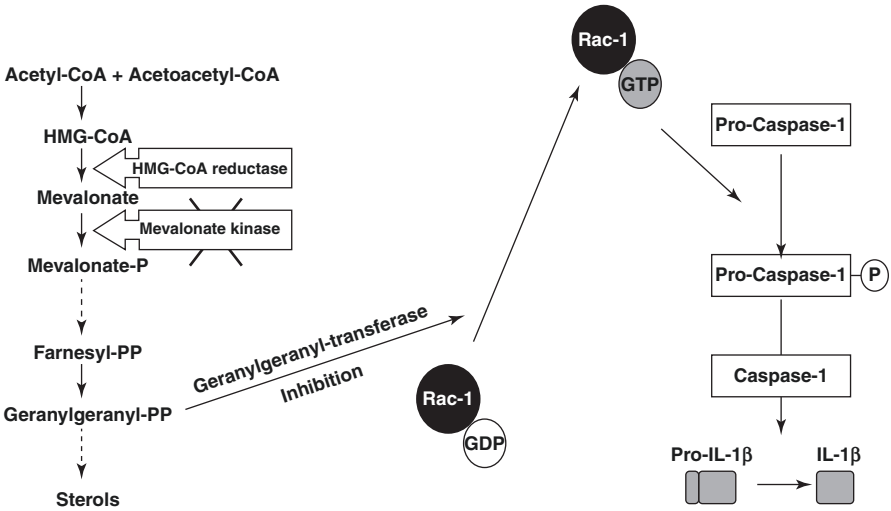

Fig. 2.1 Hypothetical pathogenesis of HIDS. Adapted from Normand et al. [35]. HMG-CoA 3′-hydroxy-3′-methylglutaryl coenzyme A; PP pyrophosphate, GDP guanosine diphosphate, GTP guanosine triphosphate, IL interleukin. (Adapted from Kostjukovits et al. [18])

synoviocytes. This finding also mirrored in MVD and could offer an explanation for the beneficial effect of statins seen in patients with HIDS as well [16].

A deficiency of MVK resulting in shortage of the isoprenoid downstream compounds leads to systemic inflammation through mediation by interleukin (IL)-1β [17]. Lack of geranylgeranyl phosphate leads to caspase-1 activation through Rac1 signaling and subsequent conversion of pre-IL-1β to an active IL-1β (Fig. 2.1) [18].

In another observational study, it was determined that the increased cytokine response in HIDS patients is specific for TLR4, TLR2, and NOD2 ligation and involves other pro-inflammatory cytokines along with IL-1b. Exposing PBMCs from patients with HIDS to LPS (TLR4 ligand) for 24 h in this study resulted in increased IL-1α and IL-1β secretion, while stimulation with TLR2 (Pam3Cys) and NOD2 (MDP) ligands lead to increased IL-1α, IL-1β, IL-6, and TNF secretion. Authors assumed that more easier secretion of IL-1b resulted in the increased ratio between active and inactive caspase-1 protein in HIDS patients. The study favored multi-cytokine mechanism in HIDS pathophysiology [19].

Organ Manifestations

The most common clinical characteristics of the disease are fever above 103F which can last up to 3–7 days with periods of well-being between the cycles, lymphadenopathy mainly in cervical region, aphthous ulcers, gastrointestinal symptoms (nausea,

Table 2.2 Frequency of most common clinical manifestations of HIDS from three largest cohorts

Symptoms	% of patients 103 patient cohort by van der Hilst et al. [12]	% of patients 114 patients by Ter Haar et al. [13]	% of patients 23 patients by Durel et al. [4]
Skin lesions	68.9	Maculopapular rash 39 Urticarial rash 15	82.6
Lymphadenopathy	87.4	85	82.6
Hepato/ splenomegaly	Hepatomegaly 21.6 Splenomegaly 32.4	38	47.8
Arthralgia	83.5	71	87.0
Arthritis	55.3	28	47.8
Abdominal pain	85.4	88	82.6
Diarrhea	71.6	84	47.8
Vomiting	70.9	69	30.4
Headache	63.3	38	34.8
Aphthous ulcers	48.5	60	30.4

vomiting), maculopapular rash, and arthralgias. Other symptoms such as headache, shortness of breath, chest pain, and splenomegaly have been reported [12].

The most common manifestations outlined in Table 2.2 can be grouped by organ systems as follows:

Systemic Complains Periodic febrile attacks lasting up to a week at a time are more common in childhood. Even though severity and frequency of attacks may subside with age with very few or no attacks off treatment in some cases, in majority of the patients, fevers rarely resolve completely [12]. Most of the time, patients remain symptomatic, experiencing more than six febrile attacks per year. A French and Belgian study reported nearly 55% of their patients surviving into adulthood with severe disease (disease activity scores of 2), characterized by frequent severe febrile episodes with major organ involvement [20].

Skin and Mucous Membranes Skin manifestations of HIDS vary from most commonly reported maculopapular eruption, urticaria, and periorbital erythema to rare cases of erythema nodosum and purpura. Aphthous ulcers and pharyngitis are typical during the attacks.

Lymphadenopathy Lymphadenopathy is seen in almost 90% of the patients during attacks. The enlarged lymph nodes were generally located primarily in the cervical region. Axillary and inguinal lymphadenopathy is less frequent [13].

Splenomegaly and Hepatomegaly Hepatosplenomegaly is highly prevalent in majority of HIDS patients. From the published reports, it was found in >30% of cases, with majority of the patient experiencing accompanying lymphadenopathy. International HIDS database reports 22% of patient experiencing isolated hepatomegaly. A few pediatric cases report cholestatic hepatitis.

Gastrointestinal Symptoms Most common GI symptoms of HIDS are flares of abdominal pain, vomiting, and/or diarrhea happening in parallel with febrile attacks and occasionally resembling acute abdomen in most severe cases. Occasional cases of aseptic peritonitis and abdominal adhesions have been reported.

Musculoskeletal Involvement Inflammatory polyarthritis and arthralgia affecting predominantly large peripheral joints and hand joints in RA distribution (MCPs and PIPs) are highly prevalent in HIDS. In some larger published reviews, inflammatory polyarthritis was observed in over 50% of the patients and arthralgia was present in 83.5% of HIDS cases [12].

A handful of cases of osteitis, contractures, and bone deformities have been reported [13].

Myalgias are not uncommon and were described in close to 50% of HIDS patients. No cases of inflammatory myopathy were reported to date.

Neurologic Manifestations CNS involvement is not uncommon in MVD. Cases of mental retardation, retinitis pigmentosa, and cerebellar disease that are more prevalent in severe phenotypes (MVA) where disease manifested in childhood [13, 21].

In HIDS cases headaches, dizziness, and mood disorders are common during the attacks, and in some 25% tend to happen in periods between the attacks. Etiology of mood disorders remains obscure, although psychological impact of the disease tends to play a role.

Rare Manifestations

Macrophage activation syndrome and AA amyloidosis tend to be uncommon in HIDS and were described in only a handful of case reports. The first patient with amyloidosis in HIDS was described by Obici et al. [22] in a case report of a 27-year-old male of Italian descent. In this case the patient presented with proteinuria accompanied by febrile attacks which lasted 3–7 days, lymphadenopathy and abdominal symptoms. Kidney biopsy with Congo red stain confirmed AA amyloidosis. In this patient, two mutations in the mevalonate kinase gene were identified, one of which, the leucine-to-arginine substitution at codon 265, was novel.

Pseudotumors are very uncommon to HIDS but nonetheless described in a few cases. One of the case studies reported an 11-year-old patient with several hypoechoic pseudotumoral hepatosplenic masses. Similar nodular lesions, suggestive of metastases, disseminated in the liver and spleen as well as lung consolidations were detected with the thoracoabdominal CT (T1-weighted). Extensive screening for infection was nevertheless negative and empiric antibiotic therapy unsuccessful. The lesions were completely reversible with corticosteroids [23].

A few reports of *pneumonia and interstitial lung disease* were described but not widely prevalent in HIDS.

Another rare complication reported in HIDS was pauci-immune crescentic glomerulonephritis [24]. Glomerular inflammation was believed to be induced by HIDS-related cytokine release. Larger cohort studies did not observe glomerular disease in HIDS.

Pregnancy

HIDS in pregnancy has not been described vastly, mostly because based on available data, HIDS does not cause any complication during pregnancy, labor, and postpartum, nor it is known to cause disturbance in fetal outcome. Interestingly enough frequency of febrile attacks tends to subside during pregnancy. Nausea and vomiting were described in certain cases, which can make differential with hyperemesis gravidarum difficult. Immunoglobulin D levels tend to remain high in pregnant women with HIDS. Due to relatively mild manifestations during this time, HIDS rarely requires treatment during pregnancy [25].

Laboratory parameters although nonspecific include increased level of acute-phase reactants (ESR, CRP, ferritin, SAA) during febrile attacks. High-serum interleukin-1 and interleukin-6 and TNFa and increased level of IgD (>140 mg/dl) along with high level of mevalonic acid in the urine during the attacks comprise more specific laboratory findings. Increase in Ig A levels was noted in some cases as well [26].

Genetic confirmation of the defect in the protein coding for mevalonate kinase enzyme is a gold standard in diagnosis of HIDS [26]. Less commonly used immunoblot analysis was performed in some cases and demonstrated a deficiency of MK protein in patient fibroblasts, indicating a protein-destabilizing effect of the mutations [27].

Treatment

There is no standard therapy for MKD/HIDS and treatment protocols have changed since the last decade. Conventional DMARDS, such as methotrexate, azathioprine, tacrolimus, dapsone, and intravenous immunoglobulins, demonstrated very limited success in HIDS.

Corticosteroids are useful in management of acute febrile attacks but demonstrate suboptimal efficacy in prevention subsequent flares. One larger cohort reports only 24.4% patients with good response and 37.8% with some response in reduction in severity and duration of attacks with continuous use of steroids [12].

Observational study by Durel et al. showed limited efficacy of colchicine, NSAIDs, and HMG-CoA reductase inhibitors in treatment of HIDS [4]. In some milder cases, zaragozic acid A demonstrated efficacy, suggesting a role for modulation of isoprenoid biosynthesis in treatment of HIDS [28].

Published reports have suggested notable decrease in disease activity and decrease in inflammatory markers with a TNF receptor blocker etanercept. Data varies from report to report and no large trials are available. It is known that onset of action of etanercept may be delayed up to 36 h, and even though severity of the attacks decreases, etanercept does help achieve full remission in many instances. The retrospective analysis of data on both adult and pediatric cases form the Eurofever registry revealed more patients responded to IL-1 inhibitor anakinra (89%) than to etanercept (65%) [29].

IL-1 blocking agent should be preferred in patients with frequent attacks and in patients with chronic active disease and long-term complications. Some studies suggest dose escalation of IL-1 agents should be tried first before switching to other biologic therapies [30].

Anakinra (a recombinant, human IL-1 receptor antagonist) was first described to reduce the overall number and severity of febrile attacks in a 7-year-old girl with MKD in 2006 [31]. Two prospective trials and others series confirm the effectiveness of anakinra in MKD [20]. In retrospective analysis of 67 MKD patients from Eurofever cohort anakinra therapy resulted in impressive responses in 89% of the patients. However, complete remission was observed in much smaller percentage of the patients (22%).

Canakinumab, a human immunoglobulin G1 monoclonal antibody directed against IL-1b, has been extensively studied in the treatment of HIDS in the last decade. There have been studies showing improvement of the febrile attacks and also some cases of complete remission.

Most recently phase 2 open-label single-arm study with two treatment phases and one withdrawal phase has demonstrated complete response (physician's global assessment of disease activity score of 0 or 1 and C-reactive protein levels less than 10 mg/liter) to canakinumab in all nine patients enrolled in the study [32].

Recent literature suggests targeting the IL-6 pathway being effective in HIDS. Larger studies are lacking, but there have been a few reports supporting use of humanized monoclonal antibody against IL-6R tocilizumab in HIDS patients with inadequate response to IL-1 [beta] or TNF-[alpha] [33, 34].

Conclusion

MKD, a rare monogenic autosomal recessive auto-inflammatory disease resulting from loss of function mutation in MVK gene, presents with the spectrum of disorders from milder HIDS to severe and often life-threatening mevalonic aciduria (MVA). While MVA can lead to death in early childhood, HIDS in general does not reduce life expectancy. Regardless of spectrum of the disease, MKD has negative impact on patient's daily activities, education, and employment. Early diagnosis and treatment may improve quality of life and prevent long-term complications and irreversible organ damage. Development of effective targeted therapies remains one of the main unmet needs in management of MKD.

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