Mevalonate Kinase Deficiency

17

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Abstract

Mevalonate kinase deficiency (MKD) is a rare autoinflammatory disease caused by loss of function mutations in both alleles of *MVK*, the gene encoding the enzyme mevalonate kinase. Deficiency of this enzyme results in impaired isoprenoid biosynthesis. The inflammatory attacks in MKD are characterized by fever, lymphadenopathy, gastrointestinal symptoms, aphthous ulcers, rash, arthralgias and/or arthritis. Severely affected patients may in addition have neurological involvement, cataract, uveitis, and failure to thrive, often dying in early childhood. This severe end of the phenotypic spectrum is called mevalonic aciduria (MA) as opposed to the milder phenotype also known as hyperimmunoglobulinemia D periodic fever syndrome (HIDS). In this chapter, we detail clinical phenotype and pathophysiological background as well as treatment options.

Keywords

Mevalonate kinase deficiency · Mevalonic aciduria · Periodic fever
Hyperimmunoglobulinemia D syndrome
Autoinflammatory · Isoprenoid metabolism

Abbreviations

CAPS	Cryopyrin-associated periodic syndrome
CRP	C-reactive protein
DSAP	Disseminated superficial actinic porokeratosis
EMA	European Medicines Agency
FDA	Food and Drug Administration (FDA)
FDPS	Farnesyl diphosphate synthase
FMF	Familial Mediterranean fever
GC-MS	Gas chromatography-mass spectrometry
HIDS	Hyperimmunoglobulinemia D syndrome
HMG-CoA	Hydroxymethylglutaryl-coenzyme A
IgD	Immunoglobulin D
IL-1	Interleukin-1
MA	Mevalonic aciduria
MK	Mevalonate kinase

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P. J. Hashkes et al. (eds.), *Textbook of Autoinflammation*,
https://doi.org/10.1007/978-3-319-98605-0_17

MKD	Mevalonate kinase deficiency
MVD	Mevalonate decarboxylase
MVK	Mevalonate kinase gene
NSAIDs	Non-steroidal anti-inflammatory drugs
PBMC	Peripheral blood mononuclear cells
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, adenitis
PMVK	Phosphomevalonate kinase
SAA	Serum amyloid A
TNF	Tumor necrosis factor
TRAPS	TNF receptor-associated periodic syndrome

Key Points

- **Mevalonate kinase deficiency is an autosomal recessive disorder caused by mutations in the gene for mevalonate kinase**
- **The clinical spectrum varies from a phenotype known as hyperimmunoglobulinemia D syndrome (HIDS) to mevalonic aciduria (MA)**
- **Inflammatory episodes are characterized by fever, lymphadenopathy, aphthous ulcers, skin rash, abdominal pain, myalgia and arthralgia**
- **Other symptoms, especially in patients of the MA phenotype, include progressive cerebellar ataxia, psychomotor retardation, dysmorphic facies, liver dysfunction, hematological abnormalities and early death**
- **Treatment of inflammatory symptoms currently focusses on interleukin (IL)-1 inhibition; for severe abnormalities, stem cell transplantation may be warranted**

17.1 Introduction

Mevalonate kinase deficiency (MKD) is an autosomal recessive disorder linked to two clinical phenotypes, mevalonic aciduria (MA, MIM610377) and hyperimmunoglobulinemia D syndrome (HIDS, MIM 260920), as the ends of a spectrum of disease, where many patients present with an overlap of symptoms. It is in some ways a unique autoinflammatory syndrome, since it combines the inflammatory features with those of an inborn error of isoprenoid metabolism.

17.2 Epidemiology

MKD is very rare. International series of patients, including the Eurofever registry (see Chap. 14) generally contain less than 200 patients [1, 2]. A German pediatric surveillance study involving 370 children's hospitals identified 16 cases of MKD in a 3-year period, resulting in an estimated incidence of MKD at 0.39 per 1 million person-years in Germany [3]. Approximately 75% of patients with MKD in the registries are from Western Europe, and 50% are from the Netherlands and France [2] or from Italy and the Netherlands [1]. Most MKD patients are of Caucasian origin. These observations can be explained partly by a founder effect [4]. In the Netherlands, the carrier frequency of the most common mevalonate kinase mutation is 1:153 [5]. There is also likely to be a reporting or recognition bias [1]. Males and females are affected equally [1, 2, 6].

17.3 Etiology and Pathogenesis

Key Points

- **Mevalonate kinase deficiency (MKD) is caused by loss of function mutations in both alleles of *MVK***
- **MKD impairs isoprenoid biosynthesis**
- **Shortage of the isoprenoid geranylgeranylpyrophosphate affects small GTPases**
- **Impaired function of the small GTPase RhoA activates the pyrin inflammasome**
- **Interleukin (IL)-1β is an important mediator of inflammation in MKD**

17.3.1 Etiology

MKD is an autosomal recessive inborn error of metabolism. Loss-of function mutations in *MVK* give rise to a reduced function of the biosynthetic enzyme mevalonate kinase [7, 8]. Over 200 sequence variants have been reported in *MVK*, of which 194 are possibly or certainly disease associated. Mutations occur in all 11

exons of *MVK* and range from single amino acid substitutions to frame shift mutations and premature termination [9]. Some mutations are incompatible with the production of any enzymatically active protein. However, such null mutations are never observed in a homozygous state, but only in compound heterozygosity with milder mutations. This indicates that some residual enzyme activity, however small, is required for intrauterine survival. Residual enzyme activity in these cases may be below the lower limit of detection. Such severely deficient individuals often present with the severe (MA) phenotype. Combinations of milder mutations that result in a residual MKD between 1% and 15% commonly give rise to a pure autoinflammatory phenotype, known as HIDS [10, 11]. The most common of these is the c.1129G > A (p.V377I) variant. The change of valine to isoleucine allows for considerable residual enzyme activity. The phenotype in individuals homozygous for this mutation ranges from clinically unaffected (personal observations) to frequent severe inflammatory attacks. Heterozygous carriers are clinically unaffected.

Mevalonate kinase enzyme is present in the cytoplasm of all nucleated cells. Its physiological function is to catalyze the conversion of mevalonate to phosphomevalonate, a crucial step in the isoprenoid biosynthesis pathway. The isoprenoid pathway yields many lipid products. These include cholesterol and all sterols derived from it, as well as the non-sterol isoprenoids. The latter are linear polyunsaturated hydrophobic molecules of varying length that can be covalently attached to target proteins (Fig. 17.1). The transfer of such hydrophobic groups to specific proteins is a post-translational modification known as protein isoprenylation. Isoprenyl groups are essential for the subcellular localization and function of proteins like the small GTPases Ras, Rac, and RhoA [12].

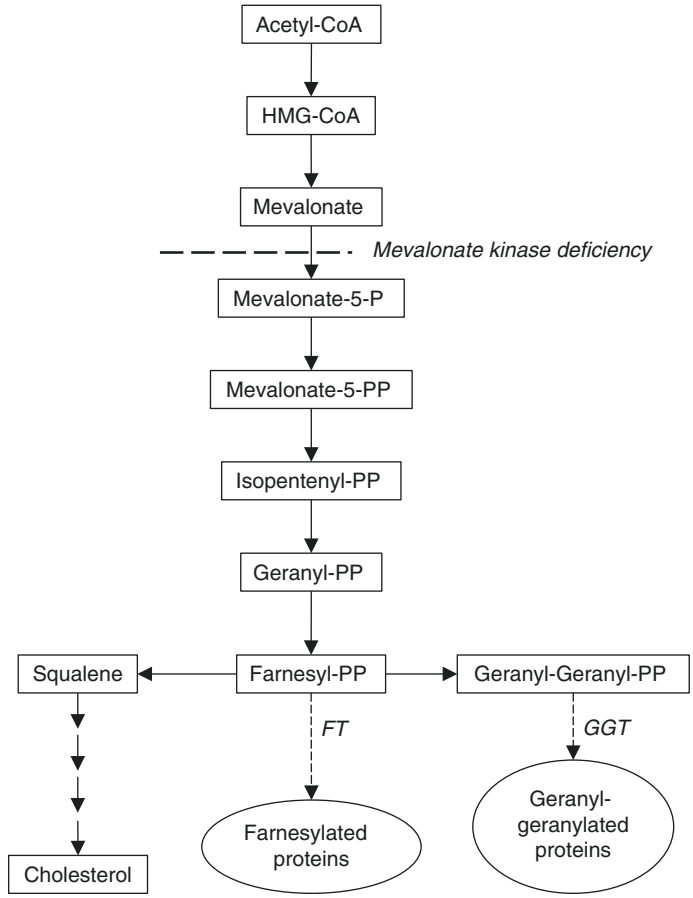

Fig. 17.1 Isoprenoid biosynthesis pathway. Acetyl-CoA is converted to hydroxy-methyl-glutaryl (HMG)-CoA and subsequently to mevalonate, the substrate of mevalonate kinase. The block in mevalonate kinase deficiency is indicated by the horizontal dashed line (------). Mevalonate kinase deficiency (MKD) leads to accumulation of its substrate, mevalonate and shortage of end-products, notably geranylgeranyl pyrophosphate. Geranylgeranyl transferase (GGT) and farnesyltransferase (FT) covalently link the respective isoprenoid groups to target proteins

17.3.2 Pathogenesis

MKD leads to the accumulation of the mevalonate kinase substrate, mevalonate, as well as reduced production of isoprenoid end-products and hence a shortage of isoprenylated proteins [13, 14]. The accumulated mevalonic acid is excreted in the urine. Its presence in urine during attacks supports the diagnosis of MKD [15].

The clinical phenotype is highly variable and is loosely related to the severity of enzyme deficiency [6, 11]. The mechanism by which the metabolic defect gives rise to the clinical and immunological features of the disease is only partly understood.

Interleukin (IL)-1β is an important mediator of inflammation in mevalonate kinase deficiency as reflected by the favorable effect of treatments which cause IL-1 blockade [16]. However, there are likely to be other mechanisms involved, since IL-1 blockade is less successful in preventing symptoms than in purely IL-1 mediated disease such as the cryopyrin-associated periodic syndrome (CAPS). Serum γ-interferon rises during attacks [17], as do tumor necrosis factor (TNF)-α and IL-6 [18]. In addition, patient mononuclear cells stimulated ex vivo produce not only excess IL-1β, but also TNF-α, especially when studied during inflammatory attacks [18, 19].

There is currently no satisfactory explanation for the pathogenesis of the neurologic, ocular and renal problems that may occur in severely affected individuals. There are two possible mechanisms by which MKD could promote inflammation: excess of the accumulating substrate mevalonate and shortage of end-products of the isoprenoid biosynthesis pathway.

Several lines of evidence suggest that it is the shortage of one specific non-steroid isoprenoid, geranylgeranyl-pyrophosphate, which is responsible for the inflammatory features of the disease. The hyper-secretion of IL-1β by patient cells can be abolished by exogenous geranylgeranyl pyrophosphate. Conversely, mononuclear cells from healthy controls produce excess IL-1β when protein geranylgeranylation is blocked [20, 21].

Recently, it was shown that geranyl-geranylated RhoA was required to silence pyrin, the protein affected in familial Mediterranean fever. RhoA acts via protein kinase N which phosporylates pyrin to allow binding of inhibitory 14-3-3ε proteins. Shortage of geranyl-geranylated RhoA results in the assembly of pyrin-inflammasomes and hence the proteolytic activation of IL-1β. In cells from individuals deficient in mevalonate kinase, either exogenous geranylgeranyl pyrophosphate or bypassing RhoA by direct activation of protein kinase N restores the binding of inhibitory 14-3-3ε proteins to pyrin and reduces IL-1β secretion to normal [22].

Other mechanisms by which mevalonate kinase deficiency may contribute to inflammation include defective isoprenylation of the small GTPase Kras, which in turn leads to a PI3-kinase-AKT mediated activation of the NFκB transcription pathway [23]. Finally, it has been suggested that shortage of a leukocyte specific steroid end-product of the isoprenoid biosynthesis pathway, 25-hydroxy cholesterol, could lead to enhanced transcription and proteolytic activation of IL-1β [24, 25].

Excess mevalonate within mononuclear phagocytes might also contribute to the inflammatory phenotype of MKD. Mevalonate was shown to induce trained immunity in murine monocytes, i.e. an epigenetically altered state leading to increased production of pro-inflammatory cytokines TNFα, IL-6 and IL-1β [26].

As for the role of immunoglobulins in MKD, serum IgD as well as IgA may be highly elevated in many patients with MKD. It is unknown how the metabolic defect gives rise to this. The physiological role of serum IgD is poorly understood as is its role, if any, in the pathogenesis of inflammation in MKD remains unknown.

17.4 Clinical Manifestations

Key Points

- **Inflammatory episodes in MKD are characterized by fever, lymphadenopathy, abdominal pain, arthralgia, myalgia, aphthous ulcers and rash**
- **In the MA phenotype, patients also suffer from progressive cerebellar ataxia, psycho-**

motor retardation, dysmorphic features, liver dysfunction and hematological abnormalities

- **Some familial forms of porokeratosis have also been associated with mutations in the mevalonate kinase gene**

MKD is classically described as consisting of two different phenotypes, the more severe MA and the less severe HIDS. It is important to realize that in clinical practice it is rather a continuous spectrum of disease severity. However, for the sake of clarity we will describe the two phenotypes at the extreme ends of the spectrum.

17.4.1 Hyperimmunoglobulinemia-D Syndrome (HIDS) Phenotype

HIDS is a disease characterized by exacerbations, commonly described as 'fever/inflammatory attacks', and symptom-free periods of remission. A typical inflammatory attack of HIDS lasts about 4–6 days, although shorter and longer attacks occur. The usual age of onset of the inflammatory attacks is before the end of the first year of life, although in rare cases and milder phenotypes, a later age of onset has been reported [1, 2, 27].

Sometimes, patients recognize prodromes like general malaise and fatigue. Chills are often an early sign of an attack, followed by a rapid rise in temperature. Accompanying signs and symptoms of an attack (Table 17.1) include tender cervical lymphadenopathy and abdominal pain with vomiting and diarrhea [1, 2, 6, 27].

Table 17.1 Accompanying signs and symptoms during an inflammatory attack of mevalonate kinase deficiency (MKD)

• Lymphadenopathy, splenomegaly, hepatomegaly
• Abdominal pain, diarrhea, vomiting
• Arthralgia, arthritis, myalgia
• Erythematous skin lesions
• Aphthous ulcers
• Headache
• Pharyngitis
• Conjunctivitis

Many patients have large joint arthralgia or arthritis. Oral or genital aphthous ulcers can occur. Skin lesions are common, and may include erythema, papules, purpura or urticaria-like rash (Fig. 17.2).

Rare accompanying signs or sequela of an inflammatory attack include pericarditis, macrophage activation syndrome [1, 6], erythema nodosum, uveitis or protracted fever and inflammation. In some patients, a severe inflammatory attack may be accompanied by frank colitis, which in rare cases has even been described as the presenting feature [28].

Hepatosplenomegaly may be present, especially prominent during an inflammatory attack; on imaging, hypodense lesions may be seen in either, which disappear during remission [29].

Ophthalmic features include retinitis pigmentosa and cataract [30], though rare (e.g. 2–3% reported in the Eurofever series [1]) and less severe than in the MA phenotype.

The series by Bader-Meunier et al. [6] reported recurrent infections in 13 of 49 patients with MKD (which included both MA and HIDS phenotypes), including otitis media, sinusitis and pneumonitis. Infections can be hard to distinguish from inflammatory attacks.

The frequency of attacks varies within and between patients. On average attacks occur every 4–6 weeks. The frequency tends to be highest in early childhood, and attacks may decrease later in life although this is not always the case. Factors that can trigger an attack include vaccination, infection, trauma and both physical and emotional stress, though often there is no clear trigger [1, 2, 6, 27]. It is characteristic in HIDS that the first attack is triggered by a childhood vaccination, with an age of onset in the first year of life. Growth and development in children with HIDS is typically normal.

Not much is known about fertility in men or women with HIDS. During pregnancy, women usually experience a significant reduction in disease activity. Childbirth can be a trigger for an attack of HIDS in the mother (personal observations).

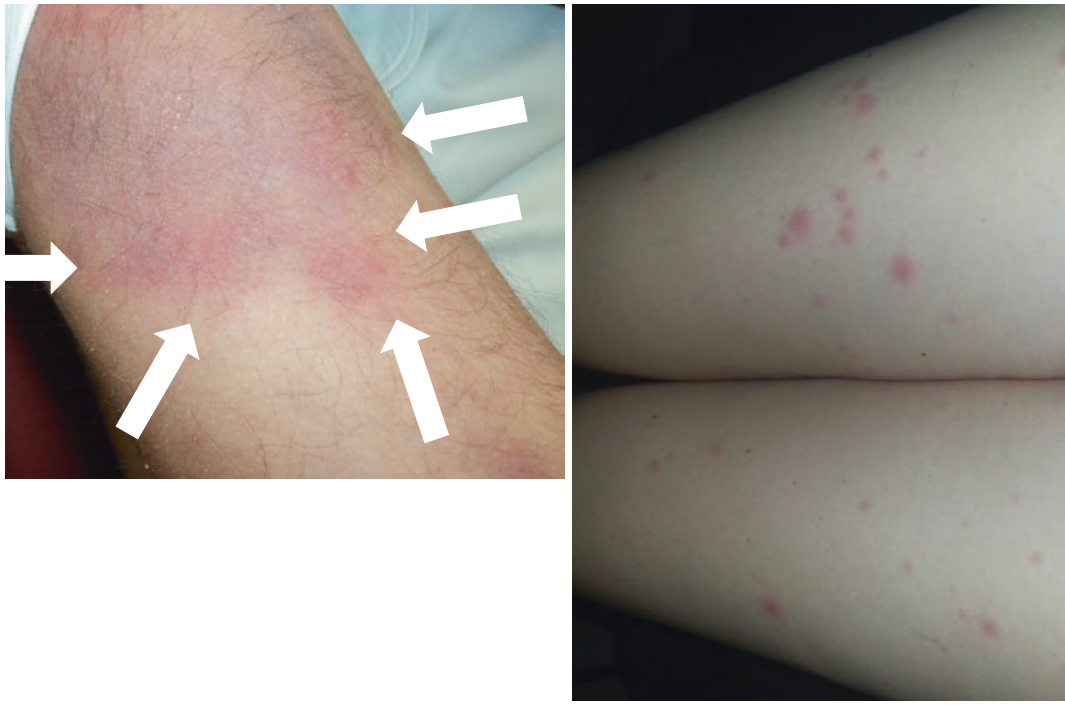

Fig. 17.2 Skin lesions as seen in inflammatory attacks of mevalonate kinase deficiency (MKD)

17.4.2 Mevalonic Aciduria (MA) Phenotype

Severe inflammatory attacks, as seen in HIDS, are also experienced by patients with severe MA. In addition, these patients suffer from continuous symptoms and signs from birth, which are often very severe [31]. These symptoms include psychomotor retardation (varying from mild to severe), progressive ataxia and dysarthria with cerebellar atrophy (developing after infancy), muscular hypotonia, failure to thrive, and cataracts. Patients with MA can have facial dysmorphic features including dolichocephaly, frontal bossing, posteriorly rotated, low-set ears and down-slanted eyes [31]. Hepatosplenomegaly and lymphadenopathy are common, becoming more prominent during inflammatory attacks. Cholestatic liver disease may be present [32, 33]. Sometimes, severe hematological abnormalities are prominent, including anemia and thrombocytopenia [33]. These may indicate the development of macrophage activation syndrome.

Many patients with MA die in early childhood; in Hoffmann's series of 11 children with MA, 4 patients died within the first 4 years of life [31].

In patients with MA, a progressive cerebellar atrophy, which develops after infancy, can be seen on neuroimaging [31]. Neurological follow-up is recommended in these cases. Retinitis pigmentosa may develop and warrants regular ophthalmologic assessment in MA.

17.4.3 Other Clinical Phenotypes Associated with Mutations in Mevalonate Kinase

Rare cases of seemingly isolated retinitis pigmentosa linked to MKD have been described [34], although detailed medical history revealed mild episodes of inflammation in childhood in some of those patients, or signs of ataxia.

Apart from these systemic syndromes, the skin disorder porokeratosis has been linked with heterozygous mutations in the mevalonate kinase gene, inherited in an autosomal dominant manner

[35–38]. Porokeratosis is a disorder of keratinization, characterized by atrophic macules or patches. Other patients with this skin disorder have been found to carry mutations in other genes in the mevalonate pathway, including those for phosphomevalonate kinase (PMVK), mevalonate decarboxylase (MVD) and farnesyl diphosphate synthase (FDPS) [36]. There are several clinical types of porokeratosis 3 (MIM175900), including disseminated superficial actinic porokeratosis (DSAP) and porokeratosis of Mibelli. These patients do not have fever or other extracutaneous symptoms. The mutations seem to lead to reduced expression of the mutant alleles, so presumably reduced activity of the isoprenoid pathway.

17.5 Laboratory Investigations

The inflammatory attacks in MKD are characterized by a high acute phase response, with very high concentrations of C-reactive protein (CRP), serum amyloid A (SAA), and elevated erythrocyte sedimentation rate (ESR). Leukocytosis with distinct neutrophilia is seen. These typically return to normal between attacks, but subclinical or minimally symptomatic inflammatory episodes can occur.

In the MA phenotype, severe hematological abnormalities and liver function abnormalities can also occur, which are usually persistent [32, 33].

Many patients with MKD, but by no means all, have high serum concentration of IgD and/or IgA [39–41]. This does not increase further during inflammatory attacks [42], and serum IgD or IgA concentrations are not correlated to disease severity. A French study included 50 patients referred to one center because of symptoms resembling the HIDS phenotype of MKD, of whom 24 did have MKD mutations, and 26 did not have MKD [41]. They found 19 out of 24 patients with MKD had high serum IgD (sensitivity 79%), while 19 out of 26 patients without MKD also had high serum IgD (specificity 27%) [41]. There is no role for repeat measurement of these immunoglobulins in the routine follow-up of patients.

AA amyloidosis is a rare but severe complication of MKD (see Sect. 17.8, and Chap. 15). For early detection of the first signs of AA amyloidosis it is recommended to check for proteinuria on an annual basis.

17.6 Diagnosis

The first steps in the diagnostic process are taking a detailed medical history, and preferably seeing a patient during an inflammatory attack. During an inflammatory attack, an acute phase response should be detectable; if there is no raised CRP, the diagnosis of MKD can be excluded. Serum IgD or IgA concentration can be determined as an intermediate step in diagnosis, but sensitivity and specificity, as previously noted (Sect. 17.5) are low [41].

An evidence-based clinical criterion to safely exclude the diagnosis of MKD and prevent unnecessary further diagnostic procedures for MKD was developed in a cohort of 149 French patients (among whom 35 had MKD), and validated on 93 Dutch patients (of whom 28 had MKD) [43]. This study showed that the diagnosis of MKD can be excluded in patients who had their first fever attack at age of 5 years or higher in combination with an attack duration of more than 14 days or absence of joint pain [43].

Patient data from the Eurofever database was used to generate evidence-based clinical classification criteria within a group of autoinflammatory disorders, including MKD [44] (see Chaps. 11 and 14). This is a statistical scoring system based on clinical features observed during typical inflammatory attacks (with exclusion of intercurrent infections or other comorbidities). For MKD, the criteria were age at onset <2 year (10 points), aphthous stomatitis (11 points), generalized enlargement of lymph nodes or splenomegaly (8 points), painful lymph nodes (13 points), diarrhea sometimes/often (20 points), persistent diarrhea (37 points) and absence of chest pain (11 points). At a cut-off sum of 42 points or more, this set of criteria gave a sensitivity of 93% and specificity

of 89% in the validation cohort [44]. These criteria should only be used after careful exclusion of other causes of fever and inflammation, such as infections, immunodeficiency, malignancy or other immunologic conditions. These criteria can help to direct further diagnostic testing in patients with a suspected autoinflammatory disease.

To confirm a diagnosis of MKD, it is necessary to either find evidence for decreased MK enzyme activity, or to detect two pathogenic mutations in the gene for the enzyme. The preference for either method depends largely on availability of diagnostic tests. The genetic test is the most readily available.

There are two main methods to examine MK enzyme activity. The first is to determine the amount of mevalonic acid, the substrate for MK, in the urine. In MA, the urinary mevalonic acid concentration is usually persistently very high, and easily detected. However, in patients with the HIDS phenotype, the mevalonic acid spike in the urine will only be detectable during an inflammatory episode [45–47], and requires a sensitive method such as gas chromatography-mass spectrometry (GC-MS) [15]. One retrospective study in a single expertise center found a sensitivity of 92% and a specificity of 90% for detection of increased urinary mevalonic acid, when compared to the gold standard of genetic mutations in the *MVK* gene [15]. The range of mevalonic acid excretion in the urine in patients with MKD (with HIDS phenotype) in this study was from 1 to 5000 mmol/mol creatinine [15].

The second method is to determine the enzyme activity directly in patient-derived cell lines, such as Epstein Barr virus-converted lymphoblast cell lines or immortalized fibroblast cell lines. This is commonly only done in research setting, but can be diagnostic.

A recent study showed that defective protein prenylation, as demonstrated with a prenylation assay on lysates from peripheral blood mononuclear cells (PBMCs) from patients, could be a diagnostic marker as well [13]. This needs further study, and is currently available only in a research setting.

The differential diagnosis of the HIDS phenotype in MKD in young children includes periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome (see Chap. 30), other (hereditary) autoinflammatory disorders or recurrent (viral) infections. For the MA phenotype, the differential diagnosis includes other metabolic disorders.

17.7 Treatment

Key Points

- **IL-1 inhibition is currently the most effective treatment for inflammatory symptoms of MKD**
- **In severe cases, especially with neurological and/or metabolic abnormalities in young children, stem cell transplantation may be warranted**

Management of patients with MKD warrants a multidisciplinary approach (see Chap. 13) [48]. Aims of treatment include control of disease activity, prevention of disease-related damage and improvement of health-related quality of life.

17.7.1 Control of Inflammatory Episodes: Anti-inflammatory Treatment

Non-steroidal anti-inflammatory drugs (NSAIDs) may provide symptom relief during inflammatory episodes, but do not shorten the episode [48]. Especially in children, short-term corticosteroids taken as soon as the first symptoms of an inflammatory attack manifest itself, may be effective in alleviating symptoms [48], however in case of frequent episodes this may result in a high cumulative dose with detrimental effects.

IL-1 inhibition is currently the most effective treatment for the inflammatory symptoms in MKD. This has been shown in case reports and case series for continuous treatment with the short-acting IL-1 inhibitor anakinra (dose in adults 100 mg/day by subcutaneous injection; in children starting dose of 2 mg/kg/day, may increase to 5–8 mg/kg/day) [48, 49]. It has also been shown

that it is possible to treat inflammatory episodes with anakinra "on-demand", started at the first prodrome of an episode [50]. In this study, when anakinra was started as soon as the fever occurred, the episode could be shortened to 2–3 days duration [46]. In clinical practice, if patients start anakinra at the first sign of prodrome it is even more effective. "On demand" use of anakinra should only be advocated in patients with relatively infrequent episodes. At a frequency of episodes of more than 1 episode per 4–6 weeks, it is recommended to switch to continuous treatment.

The long-acting anti-IL1β antibody canakinumab has been shown to be effective in HIDS to reduce the number and severity of inflammatory episodes [49, 51–53]. An open-label phase II study assessing the efficacy and safety of canakinumab was performed in nine patients (six pediatric patients and three adults) with the HIDS phenotype of MKD [53]. Patients had to have active disease, defined as at least 3 inflammatory episodes in a 6-month period. During a 6-month treatment period with 300 mg canakinumab (or 4 mg/kg for those weighing ≤40 kg once per month), the number of inflammatory episodes per patient decreased significantly (median number of attacks 0, range 0–2), with 7 of 9 patients experiencing no inflammatory episodes for the whole period [53]. In the 24-month extension treatment period that was part of this study, in which 8 of 9 patients participated, only 8 inflammatory episodes occurred (median number of attacks per patient 0, range 0–4).

Results from a double-blind placebo controlled study indicate that canakinumab (150 mg/4 weeks) is superior to placebo with 35% of patients attaining complete disease remission within 2 weeks and persisting without attacks for 16 weeks (versus 6% on placebo). When the dose was raised to 300 mg/4 weeks the percentage of patients with complete remission increased to 57% (versus 71% of patients with colchicine-resistant familial Mediterranean fever (FMF) and 73% of patients with TNF receptor-associated periodic syndrome (TRAPS) in the same study) [16]. In a subsequent phase of the trial, patients with response to canakinumab were re-randomized to receive either canakinumab (in the dose of 150 or 300 mg depending on the previous response) or placebo, once every 8 weeks. In that phase, only 23% of patients with MKD maintained disease control (versus 46% of patients with colchicine-resistant FMF and 53% of patients with TRAPS) upon this lower dosing frequency [16]. This study resulted in an Food and Drug Administration (FDA) and European Medicines Agency (EMA) registration for canakinumab in MKD in patients ≥2 years of age, at a recommended starting dose of 150 mg once every 4 weeks for patients with a body weight >40 kg (can be increased to 300 mg once every 4 weeks if clinical response is inadequate); or 2 mg/kg once every 4 weeks in patients with body weight between 7.5 and 40 kg (can be increased to 4 mg/kg every 4 weeks if clinical response is inadequate).

In patients with MKD who do not respond to IL-1 inhibitors, inhibition of TNF (etanercept, adalimumab) or IL-6 (tocilizumab) can be tried. Efficacy of these inhibitors has been shown in several case reports and in the Eurofever data [50, 54–57].

As for oral options of treatment, colchicine and thalidomide are ineffective in MKD [48, 58]. Following the good effect of simvastatin, an inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme one step prior to mevalonate kinase (Fig. 17.1), in a patient with HIDS phenotype a placebo-controlled trial was performed in six additional patients. This trial showed a small decrease in the number of days of illness per 6 months [46], however, in clinical practice, patients do not notice a significant benefit of statins. In one patient with the MA phenotype, treatment with a statin appeared to induce a severe attack [31]. Treatment with statins is therefore not recommended in MKD. One case report showed a good effect of weekly oral alendronate in a 14-year old patient with MKD (HIDS phenotype) [59]. Bisphosphonates such as alendronate are inhibitors in the isoprenoid metabolism downstream from mevalonate kinase, which have an effect on isoprenylation; this observation needs further study.

Macrophage activation syndrome (see Chap. 33) can occur as a rare but serious complication of an inflammatory attack in MKD, especially in

Table 17.2 Reports of stem cell and/or organ transplantation in early childhood in severe cases of mevalonate kinase deficiency (MKD) with mevalonic aciduria (MA) phenotype

Symptoms prompting transplantation	Sex	Age at transplantation	Details on transplantation	Outcome	Reference [number]
Severe episodes of inflammation every 2 weeks, severe hepatosplenomegaly	M	3 years	Stem cell from HLA-identical sister, heterozygous for *MVK* mutation	Follow-up 15 months No fever episodes, size of liver and spleen reduced to normal; no further progression of neurological symptoms	Neven et al. (2007), [62]
Severe episodes of inflammation	M	8 years	Stem cell from sibling	Follow-up 16 months, no more episodes of inflammation; chronic mild graft-versus-host disease (after acute onset)	Arkwright et al. (2007), [61]
Severe liver disease, severe episodes of inflammation	F	2.5 years	Liver from deceased donor	Improvement of liver function, some neurological improvement, no effect on episodes of inflammation	Chaudhury et al. (2012), [63]
Severe episodes of inflammation (same girl as above)	F	6.5 years	Stem cell, HLA identical unrelated donor	No further inflammatory episodes	Chaudhury et al. (2012), [63]
Severe episodes of inflammation and mild psychomotor delay	M	2 years, 10 months	Cord blood, unrelated	Follow-up 5 years. No more episodes of inflammation, normal psychomotor and neurological development, normal growth	Giardino et al. (2015), [64]
Severe hepatosplenomegaly and ascites	M	6 months	Bone marrow from HLA identical sister	Died of sepsis 3.5 months after transplant	Erdol et al. (2016), [66]

HLA human leukocyte antigen, *MVK* mevalonate kinase

children and in patients with severe phenotype (towards the MA end of the spectrum) [60].

17.7.2 Stem Cell Transplantation

Successful treatment with stem cell transplantation in early childhood has been described in several cases of severe MKD at the MA end of the spectrum [61–65] (Table 17.2).

Stem cell transplantation is an option for treatment in patients with MA, with prevention of attacks of fever and inflammation, resolution of hepatosplenomegaly and hematological abnormalities, and there are also indications that it can prevent further neurological deterioration. The selection of patients and the timing of the procedure should be done in consultation with physicians experienced in the disorder.

17.7.3 Treatment of Other Symptoms, Especially in MA

Little is known about treatment options for the symptoms and signs in MA not directly related to inflammation, such as progressive cerebellar atrophy. Conflicting results are available, and only from case reports. These include experience with supplementation with several end-products or by-products of isoprenoid metabolism, such as cholesterol, ubiquinone-10, ursodeoxycholic acid and vitamin E [31].

17.8 Outcome/Prognosis

Prognosis in MA is poor with early mortality and severe developmental delay. Early stem cell transplantation seems a promising option.

However, some patients with MA survive into adulthood with limited disabilities. Patients with the HIDS phenotype have a better prognosis. In many patients, the frequency and severity of inflammatory episodes decrease in adulthood. However, a substantial proportion of patients still suffer from regular attacks of fever in adulthood.

AA amyloidosis can occur as a complication of long-term inflammation (see Chap. 15) and has been described in several patients with MKD [1, 66–69]. The percentage of AA amyloidosis in MKD is estimated to be about 4–5% (in the Eurofever series of 114 patients, 5 patients had AA amyloidosis), which is lower than in some of the other hereditary autoinflammatory syndromes [1, 67]. The reason for this lower incidence (even when only compared to patients with other autoinflammatory disorders from developed countries) is unclear. There is no genotype correlation with mutations in *MVK* or SAA genotype, and patients with MKD can also have increased inflammation markers while symptoms are in remission [70].

Progressive retinitis pigmentosa can occur. A survey of 50 patients with MKD revealed three patients who developed renal angiomyolipoma [6]. Flexion contractures and abdominal adhesions can occur as rare long-term complications of the recurring inflammatory attacks [1].

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