

Different presentations of mevalonate kinase deficiency: a case series

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Abstract

Objective

We aimed to raise awareness among paediatricians and physicians about this often misunderstood condition.

Methods

We discussed the clinical profiles associated with late or wrong diagnosis of mevalonate kinase deficiency (MKD) in a single centre case series.

Results

*We analysed the most common challenges and pitfalls that a clinician might face during the diagnostic process.
Five main clinical profiles were characterised.*

Conclusion

We propose a new perspective on MKD, suggesting that the presentation of this disease can vary from patient to patient.

Key words

hyper-IgD syndrome, mevalonate kinase deficiency, autoinflammatory syndromes, periodic fever.

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Introduction

Mevalonate kinase deficiency (MKD) is an inborn error of metabolism, which encompasses a wide spectrum of diseases, depending on the extent of the enzymatic defect and ranging from the milder Hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS, OMIM no. 260920) to severe mevalonic aciduria (MA, OMIM no. 610377). HIDS is characterised by recurrent inflammatory attacks with fever, arthralgia, rash, abdominal pain and diarrhoea occurring during early infancy. MA usually arises in the first months of life, presenting symptoms such as hepatopathy, psychomotor retardation and cerebellar ataxia, in addition to inflammatory attacks (1, 2). Although the wide clinical spectrum of the disease has been known for 20 years, it still takes an average of 10 years after the onset of symptoms to diagnose the disease (3-5).

Epidemiology and pathogenesis

MKD is a rare genetic disorder, with autosomal recessive inheritance and an estimated prevalence of around 1:100.000 (6).

The genetic defect results in a diminished activity of the Mevalonate Kinase (MK) enzyme, which is involved in the production of bioactive isoprenoids, vitamin D, ubiquinone, squalene-derived steroidal hormones and cholesterol. Mutations leading to residual MK enzymatic activity between 1% and 10% of the normal activity are associated with auto-inflammatory phenotypes, while neurological signs usually occur with mutations associated with near-absent enzymatic activity (1).

Clinical features

The development of molecular diagnostics has improved detection of MKD and definition of its clinical spectrum. In particular, patients with milder forms of the disease display a variety of clinical manifestations, which may often mimic other more common disorders as will be discussed below (Fig. 1).

MKD presenting as hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS)

Patient 1 is a 7-year-old boy who has

been suffering from a two-day recurrent fever since the age of 9 months. The attacks are characterised by mild abdominal pain and sporadic episodes of diarrhoea. In the first years of life he also developed a cutaneous erythematous rash and small oral aphthae. A cousin reported similar notable episodes. The fever responded to glucocorticoids. Laboratory investigations revealed increased WBC and acute phase reactants during attacks and strikingly high levels of serum IgA (1070 mg/dl) (n.v. IgA adjusted for age 50 ± 24 mg/dL). IgD were 64 mg/L (n.v. <141 mg/L).

This is probably the most common presentation of HIDS, with disease onset during the first year of life. Recurrent bouts of continuous-remittent fever, lasting 3-7 days are usually associated with enlarged cervical lymph nodes, pharyngitis, abdominal pain, arthralgia and variable skin rash. Diarrhoea often accompanies the episodes. Increased leukocytes, ESR and CRP are usually found during flares; levels of IgA, IgD and other classes of immunoglobulins can be extremely high. Unexplained normocytic anemia is often observed (7, 8). Although the clinical manifestations of the PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome) are common, the onset in the first months of life of severe abdominal pain, geographic-like stomatitis, systemic lymph nodes, liver and spleen enlargement should raise the suspicion of MKD (9).

MKD mimicking recurrent infections and sepsis

Patient 2 is a 7-year-old girl who has been suffering from recurrent infection-like episodes since the age of 4. Over the past 2 years, she has been referred to hospital several times. In two of the episodes, she was diagnosed with bacterial pneumonia, based on elevated CRP and on some questionable areas of hazy opacity. However, antibiotic treatment was scarcely successful. In one of the episodes, the girl was admitted to hospital under suspicion of a bacterial enteritis. During the crisis, the increase in CRP and other acute phase reactants were attributed to infection. Most of the episodes were also

Competing interests: none declared.

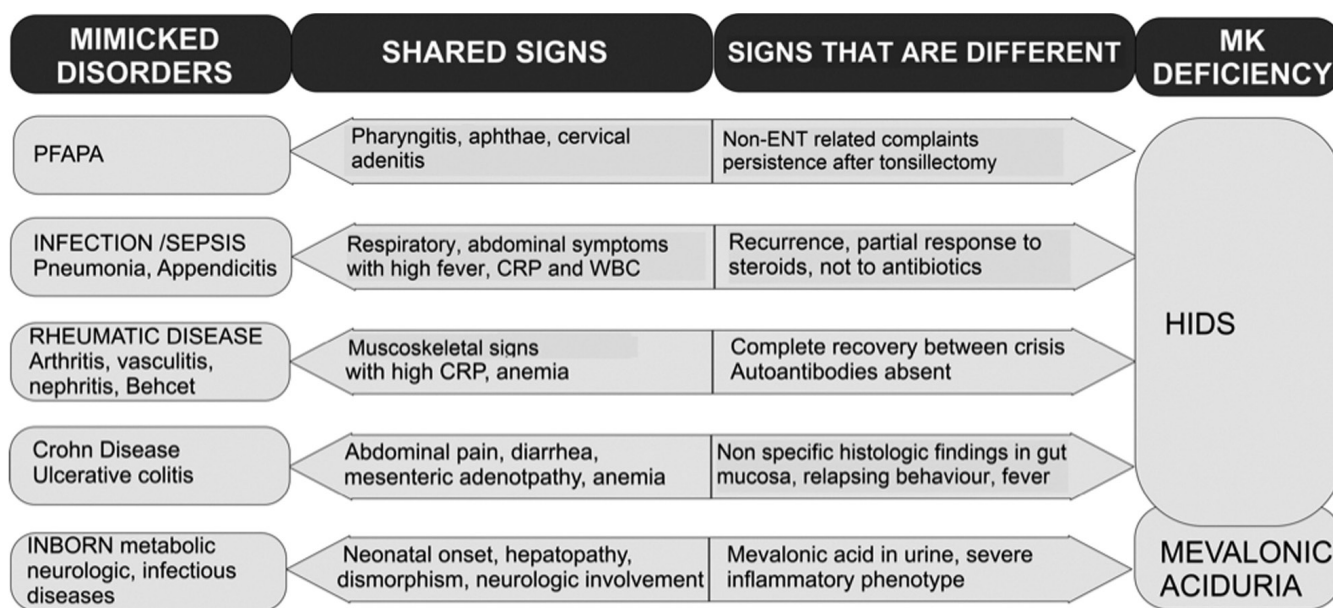


Fig. 1. Presentation patterns and differential diagnosis of MKD.

associated with oral apthae, enlarged cervical lymph nodes and sore throat. The clinical picture with recurrent fever, abdominal pain and diarrhoea led to the suspicion of an autoinflammatory syndrome. The administration of corticosteroids yielded a good response. High levels of mevalonic acid were measured in urine. The genetic analysis showed the V132I mutation and the homozygous c.1129G>A / c.1129G>A / V377I/V377I mutation, confirming the diagnosis of MKD. Patients with MKD frequently seek medical attention because of high fever of unknown origin. In infants, epi-

sodes like these are often attributed to sepsis (10). While laboratory findings, such as increased neutrophils and high CRP, would support the idea of a bacterial infection, the lack of response to antibiotics is not consistent with this hypothesis. In contrast, the recurrence of several similar episodes, seemingly unprovoked, should lead to a diagnosis of auto-inflammatory disorders. In some cases, MKD may mimic acute abdomen syndrome. Thus individuals complaining of severe abdominal pain, high fever and elevated acute phase reactants may be sent for surgery where only enlarged mesenteric lymph nodes

and non purulent appendices will be found. CRP increase and leukocytosis may lead to incorrect diagnosis of bacterial pneumonia in patients with crises occurring in the course of a common cold. These patients while not responding to antibiotics will respond, albeit in some cases incompletely, to glucocorticoids thereby suggesting that the symptoms may be due to the inflammatory reaction rather than to an underlying infection. The recurrence of episodes should prompt physician to notice other signs, such as skin rash and joint pain, which could lead to the diagnosis of MKD.

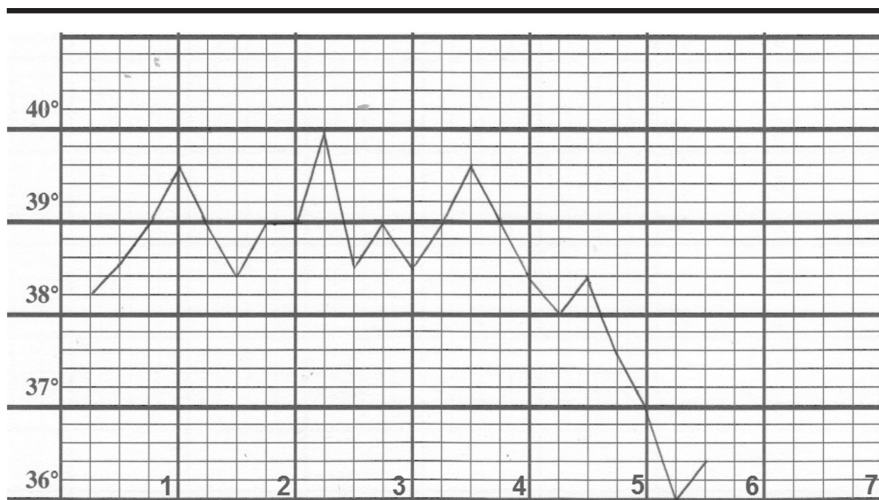


Fig. 2. A typical temperature chart during a fever attack. Time (days, each day is represented by bold vertical line): x-axis, temperature (C°): y-axis.

MKD mimicking a vasculitis or a rheumatic disorder.

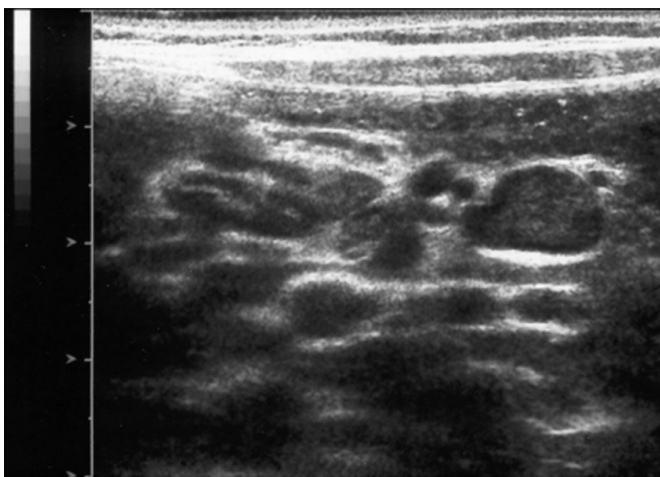
Patient 3 is a 23-year-old woman who has suffered from several crises of fever of unknown origin. Over the years, she has been admitted to different hospitals and was given various diagnoses. The disease onset was at the age of 2 months, with high fever and diarrhoea. The supposed diagnosis was milk intolerance and the therapeutic strategies were based on changing milk formulae, but with no significant benefit. One month later, she presented high fever after the administration of the diphtheria-pertussis-tetanus vaccine, and again at the subsequent vaccine booster. At the age of 6 months she developed peri-

odic fever recurring every 15–20 days, oral aphae, arthralgia, palpebral oedema and hyperaemia. A macular-papular rash and lymph node enlargement were also noted. The crises were controlled fairly successfully with the administration of glucocorticoids on demand. In the course of the following three years, she was referred to clinics for recurrent fever and in two different occasions the symptoms were consistent with Henoch-Schönlein purpura, with leg rashes and abdominal and joint pain. At the age of 9, the diagnosis of MKD was hypothesised based on laboratory findings showing high levels of IgD (989 U/ml), but genetic confirmation showing the c16_34del/V377I mutation was only possible five years later. The association of skin rash and arthritis may cause suspicion of a rheumatic disease. MKD Inflammatory attacks can occasionally present a profile which is similar to Henoch-Schönlein Purpura (HSP), with a purpuric rash, severe abdominal pain, joint pain and, rarely, proteinuria. Other cases of MKD may present with the typical symptoms of Behçet's disease, including painful mouth ulcers, pseudo-pustular skin lesions, gut inflammation, arthritis and macrophage activation syndrome (11). It has recently been shown that MKD can present with a clinical picture resembling Kawasaki disease, with protracted unexplained fever, mild conjunctivitis, some kind of skin rash and coronary arteritis. A transient response to IVIG can support the diagnosis, but the subsequent course of disease, with recurrent fever episodes will rise the suspicion of MKD (12).

MKD mimicking inflammatory bowel disease

Case 4 is a 4-year-old boy, who was referred to hospital at the age of 6 months because of a history of recurrent episodes of fever associated with strong abdominal pain, cervical lymphadenopathy, pharyngeal hyperaemia, occasional macular skin rashes and diarrhoea. The early onset of symptoms brought us to consider HIDS as a possible diagnosis but, given the low levels of serum IgD, a genetic analysis was not performed. The patient's medical history was ascribed

Fig. 3. Mesenteric lymph node enlargement on ultrasound scan.



to PFAPA and the attacks were treated with corticosteroids. Despite this, the frequency of the episodes increased and the patient underwent tonsillectomy. Nevertheless, in the course of the following months, the febrile attacks recurred, complicated by abdominal pain and bloody and mucous diarrhoea. When eventually an ultrasound scan of the abdomen was performed it showed multiple enlarged mesenteric lymph nodes and slight thickening of the bowel wall. On one occasion, the boy developed intestinal occlusion and a laparotomy was performed, showing adhesion and swollen lymph nodes, but no suppuration. An inflammatory bowel disease (IBD) was suspected and a treatment with immunosuppressant drugs, including full dose corticosteroids, methotrexate and etanercept, was started. In spite of this treatment, the boy presented recurrent flares with fever and abdominal involvement (13). At this point, because of the clinical picture and of recent evidence in literature that the disease can present normal levels of IgD, the hypothesis of HIDS was reconsidered. The patient was subsequently shown to have the c.1129G>A/c.803T>C, V377I/I268T mutations in MVK gene.

Some clinical features of MKD can be consistent with the diagnosis of IBD (3, 14). Abdominal pain with mucous diarrhoea is common in MKD, as well as bloody diarrhoea (3). MKD presenting as severe early-onset inflammatory colitis has recently been described (15). In some cases, abdominal symptoms can outlast fever, suggesting that underlying chronic disorders, such as IBD, may be

present. Laboratory findings of normocytic anaemia and of increased acute phase reactants, which are typical of a MKD crisis, can also be interpreted as the result of the chronic inflammation associated with IBD. Thus patients may be subjected to a number of invasive procedures, such as gut endoscopies, aimed at finding specific features that can confirm IBD. However, in most cases, examinations only reveal the presence of mild and non-specific inflammation. On the other hand, enlarged mesenteric lymph nodes, together with spleen and liver enlargement, are typical signs of MKD.

MKD should be considered in subjects with atypical early-onset inflammatory bowel disease, in particular if symptoms are recurrent and accompanied by fever. However, it should be noticed that, in some cases, treatment with glucocorticoids can modify the disease, hiding its periodic behaviour. If MKD is suspected, a biochemical and genetic diagnosis may prevent the patient from undergoing further diagnostic tests and ineffective or even dangerous treatments (14).

MKD presenting as mevalonic aciduria

Case 5 was diagnosed as mevalonic aciduria (MA) at the age of 4 months, based on a clinical picture that included minor facial dysmorphism, persistent fever, polymorphous skin rashes, marked irritability, lymph nodes enlargement, and diarrhoea. The genetic analysis showed a homozygous mutation in MVK gene c.60T>A, p.H20G. The clinical history that followed was characterised by the development of polyarthritis. anakinra

Table I. Summary of the clinical cases.

Case	Respiratory symptoms	Abdominal symptoms	Skin and mucosae	Articular	Laboratory findings	Surgical intervention	Mutation
1	-	+	+	±	IgA ↑ IgD normal	-	S135L/ V377I
2	+	±	-	-	Mevalonic acid ↑	-	V377I/V377I/ V132I
3	-	+++	+	++	IgD ↑ IgA ↑ Mevalonic acid ↑	Tonsillectomy	L6fs/V377I
4	±	+++	+	+	IgM ↑ Mevanonic acid ↑	Laparotomy x2 Tonsillectomy	V377I/I268T
5	-	+	++	+++	Mevanonic acid ↑		c.60T>A, H20G.

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome; MKD: Mevalonate kinase deficiency; IBD: Inflammatory bowel disease.

(1 mg/kg) and glucocorticoids were administered with a satisfactory initial response but after 8 month anakinra was discontinued because the symptoms worsened. In subsequent years, a variety of immunosuppressant drugs, including etanercept, methotrexate, cyclosporine A, intravenous immunoglobulin were used in the attempt to control symptoms. A partial control of the inflammatory disease was achieved only with high dose corticosteroids (ranging from 0.5 to 1.5 mg/kg prednisone/day). At the age of 4 years the girl developed vertebral crush fractures which precluded further use of glucocorticoids. Subsequently, anakinra (2 mg/kg) was administered again, leading to significant clinical benefit, but active arthritis persisted and the parents refused to continue the treatment because of painful injection site reactions. To date, she has developed neither cerebral impairment nor cognitive developmental abnormalities but her quality of life is significantly impaired by physical disability secondary to polyarthritis which is not responding to conventional therapies.

In typical mevalonic aciduria, auto-inflammatory attacks are present, but recurrence may be less evident compared to HIDS, and more serious neurological features tend to divert attention away from the inflammatory symptoms. Mevalonic aciduria is usually dominated (case 5 being an exception) by neurological involvement, with cerebellar ataxia and mild to severe psychomotor delay. Most severe cases of MA present with perinatal disease manifestations, including congenital malformations, cholestatic liver disease, and a charac-

teristic *facies* with low set and posteriorly rotated ears, down slanted palpebral fissures, blue sclerae, and central cataracts (16). The clinical picture may mimic bacterial sepsis in an infant with congenital malformations, and be attributed to intrauterine infections or chromosomal abnormalities. Two cases of fetal hydrops with low excretions of mevalonic acid were also described (17). However, the analysis of organic aciduria is usually sufficient to make a correct diagnosis. Some patients, who are less severely affected, may later develop progressive psychomotor retardation, ataxia, ocular involvement with uveitis and cataracts, as well as recurrent inflammatory crises (1).

Other complex phenotypes

MKD has been associated to a variety of rare manifestations, in conjunction the usual recurrent inflammatory phenotype. Nephritis, diabetes insipidus, severe dyserythropoietic anaemia, thrombocytopenia, cholestatic liver disease, persistent diarrhoea and renal angiomyolipoma have been described in patients with MKD.

Other hereditary periodic fever syndromes (HPF) that need to be considered for differential diagnosis

Other HPF syndromes may have to be considered in some cases. Useful hints for differential diagnosis have been thoroughly discussed by Drenth (18) and Gattorno (19, 20).

In particular, TNF-receptor associated periodic syndrome (TRAPS) may be considered in PFAPA-like cases with severe abdominal complaints. However,

the occurrence of specific clinical features such as long duration of episodes, muscle pain and periorbital oedema may help make the correct diagnosis.

Familial Mediterranean fever (FMF) should be considered in differential diagnosis as well, especially in subjects with fever and arthritis. This possibility should always be considered in subjects of Mediterranean ancestry. The most useful clue for a correct diagnosis of FMF is the short duration of crises (1–2 days) combined with severe abdominal and/or chest pain (21). Furthermore, inflammatory attacks in FMF usually show lower, or even absent, response to glucocorticoids compared to other HPF syndromes.

As a result of CIAS1/NLRP3 defects, other HPF syndromes can present a clinical picture which mimics a rheumatologic disorder. The early onset of fever and the presence of urticarial rashes are typical features which may lead to a correct diagnosis, when associated with sensorineural and bone involvement (22).

Conclusions

In spite of improved biochemical and genetic diagnostics, MKD may still be misdiagnosed because of its complex clinical presentation, which often mimics more common inflammatory or infectious disorders. Although MKD is a rare disorder, raising awareness of this disease among physicians could expedite diagnoses and avoid unnecessary investigations and treatments.

Even if the clinical picture may mimic other pathological conditions, the recurrent nature of the attacks should prompt suspicion of MKD.

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