CASE REPORT

Hyper-IgD and periodic fever syndrome (HIDS) due to compound heterozygosity for G336S and V377I in a 44-year-old patient with a 27-year history of fever

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SUMMARY

Hereditary autoinflammatory syndromes are a rare, but notable cause of fever of unknown origin. During the last few years, the knowledge of the genetic background has significantly increased. Here, we report a novel pathogenic mutation in the *MVK* gene as the cause of fever in a 44-year-old male patient with a history of fever over a period of 27 years.

BACKGROUND

Fever of unknown origin (FUO) remains a great diagnostic challenge for clinicians, infectiologists, oncologists and rheumatologists.[1 2]

Hereditary autoinflammatory syndromes causing febrile disorders are a heterogeneous group of different pathophysiological conditions of innate immune response. The most common diseases are familial Mediterranean fever (FMF), the tumour necrosis factor receptor 1-associated periodic syndrome (TRAPS), the cryopyrin-associated syndromes and mevalonate kinase deficiency (MKD).[3–6]

MKD is the combined term for the disorders hyper-IgD and periodic fever syndrome (HIDS), first described in the early mid-1980s,[7] and mevalonic aciduria (MA), initially described in 1985.[8 9] MA is an often fatal multisystemic disorder characterised by a neurologic clinical picture with psychomotoric retardation, ataxia, myopathy and cataract. Recurrent fever, lymphadenopathy, arthralgia, elevated IgD levels and gastrointestinal symptoms can be present in both diseases.[10 11]

MKD is an autosomal recessive disorder caused by mutations in the *MVK* gene leading to impaired enzyme activity or stability.[12 13] Mevalonate kinase is a key enzyme in isoprenoid biosynthesis,[14] and it is involved in a broad range of cellular processes.[15] The severity of the clinical picture, either mild HIDS or severe MA, is determined by the residual enzymic activity.[15] In MA, the residual activity in most cases is below detection level (<0.5%).[10 11 16] In HIDS patients, in contrast, the remaining enzyme activity is about 1–7%.[12 16] Therefore, the mevalonate concentration in serum and urine is higher in patients suffering from MA.[10 12] Both diseases "are now recognized as the severe and mild clinical ends of the MKD spectrum" (quote).[17]

If a hereditary autoinflammatory syndrome is suspected, a broad genetic diagnostic workup is still time-consuming and cost-intensive in routine clinical practice. There is often a long delay in diagnosis. Two recent retrospective analyses showed an average delay of 7.1 years in a case series of 13 French patients and of 13.9 years in an international case series.[18 19]

Here, we present a patient with a long history of fever episodes, in whom a novel mutation in the *MVK* gene could be identified. This case illustrates again a long delay in diagnosis due to insufficient knowledge of the underlying disease.

CASE PRESENTATION

A 44-year-old male patient presented to the Infectious Diseases Department in Bonn, Germany, with unexplained fever episodes, since he was 17 years old. The fever was typically present over a period of 2–3 days, but he had noticed longer attacks especially in the first years after disease onset (2–8 days). Mostly, the fever was accompanied by arthralgia in the knees as well as myalgias. On some occasions, the patient also reported headache and fatigue, night sweats and loss of appetite. During the last 10 years, he had suffered from 2 to 3 episodes per year. However, during the last 3 months before presentation, he observed approximately six episodes, sometimes only a few days apart. On presentation in our clinic, however, he showed no clinical symptoms and had a normal performance status.

His further medical history included meningitis following an umbilical sepsis at the age of 3 months, chickenpox, mumps and two pneumonias in childhood. Surgical history taking revealed appendectomy, tonsillectomy and herniotomy in childhood. He was not taking any regular medication, apart from pain relievers during the fever episodes. However, due to lack of fever relief, he did not take any drugs during the last few years. Vaccinations had been carried out against variola, polio and measles in childhood as well as tetanus, hepatitis A and B and tick-borne encephalitis virus (TBEV) after childhood.

The patient worked as a ranger. Owing to his occupation, he was frequently exposed to tick bites. His travel history involved journeys within Europe and to South Africa 1998, Canada 1991 and 1994 and Albania in 2011.

Former diagnostic workup excluded leukaemia, HIV, hepatitis C, malaria (2002), active Borrelia

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infection (1996 via lumbar puncture and again 2013) and rheumatic disease (2010). The only notable finding was an elevated factor C4 (55 mg/dL, normal 10–40 mg/dL).

INVESTIGATIONS

At presentation in our clinic, physical examination revealed a patient in a good general health condition (174 cm, 76 kg) without pathological findings of the head and neck, the thorax, the cardiovascular system, the abdomen and the musculoskeletal system. Lymph nodes were smaller than 1 cm in diameter. Ultrasound examination showed a normal organ size of liver and spleen.

Laboratory results including electrolytes, creatinine, liver parameters and ferritin were in the normal range. Blood cell count, immune status (CD4/CD8 ratio 2.86) and immunoglobulin concentration were normal. Protein electrophoresis revealed a normal distribution of plasma proteins, and immunofixation ruled out a monoclonal gammopathy. We analysed antinuclear (ANA 1:80) and antineutrophil cytoplasmatic antibodies (ANCA 1:10) and complement concentration to rule out a vasculitis. thyroid-stimulating hormone (TSH) and serologic parameters of autoimmune thyreoiditis were analysed without positive result. An antistreptolysin titre of <13 IU/mL ruled out a rheumatic fever. A normal blood cell count and a normal ratio of free light chains made a haematological disease unlikely. The erythrocyte sedimentation rate (ESR) was 5/14 mm. Noteworthy, we saw a slightly decreased concentration of α1 antitrypsine (0.7 g/L, normal 0.9–2.0 g/L). Analysis of exons 3 and 5 of the *SERPINA1* gene revealed heterozygosity for the Z mutation with the S mutation being absent.

Owing to his profession as a ranger, we performed serologic testing for Borrelia, *Coxiella burnetti*, Brucella, *Rickettsia conorii* and toxoplasmosis without any finding. Results for cytomegalovirus (CMV), HIV and hepatitis A, B and C infection were also negative.

Owing to the long clinical history and spontaneous remissions, an autoinflammatory syndrome with fever episodes was suspected. We therefore performed genetic analysis of exons 2, 3, 4, 6 and 7 of the *TNFRSF1A* (TRAPS) and exons 2, 3, 9 and 10 of the *MEFV* gene (FMF) without finding a mutation. The sequence analysis of the *MVK* gene, in contrast, showed compound heterozygosity for the amino acid substitutions glycine 336 (GGT) → serine (AGT) (p.Gly336Ser or G336S) and valine 377 (GTC) → isoleucine (ATC) (p.Val377Ile or V377I) encoded by exons 10 and 11. The underlying nucleotide exchange was c.1006G>A. On the basis of the clinical symptoms together with the genetic findings, the patient was thus diagnosed to have a hyper-IgD syndrome with periodic fever (HIDS).

TREATMENT

Owing to mild clinical symptoms, no regular medication was indicated.

A causative therapy of this fever syndrome is not known. Therefore, symptomatic treatment to lower the fever is the only available option. Episodes last livelong with a tendency towards a lower frequency and severity of attacks later in life.[19] Case reports include symptom-based treatment using statins, etanercept or anakinra.[20] Amyloidosis risk is about 1–2% to 2.9%.[19 20] Joint contractures were seen in 3.9% and abdominal adhesions in 9.7% of the cases.[19] A long-lasting therapy is generally not recommended.[20]

DISCUSSION

Hereditary autoinflammatory syndromes are a rare cause of recurrent fever. The pattern of the fever episodes and the clinical symptoms vary widely. In the case presented, genetic analysis of three frequently mutated genes was necessary for the diagnosis of HIDS.

The diagnosis was reached 27 years after onset of symptoms. In this case, rather mild clinical symptoms lead to infrequent presentation and in part may have caused this delay.

Patients suffering from MKD show first fever episodes in early childhood (<1 year).[21] In the present case, the onset occurred at the age of 17 years, which is rather late. Two case series showed an onset before the age of 3 years.[18 22] Only 6% of patients in one case series of 103 patients had an onset of the disease beyond the age of 4 years, one patient being aged 10 years.[19] In another case series, a manifestation beyond 5 years was found in only 3 of 35 patients.[22] This criterion (age >5 years) was used as an exclusion criterion for HIDS. HIDS nevertheless remains possible if the patient meets both of the following criteria: arthralgias and duration of fever <14 days. The fever attacks lasted ~3 days (4–6 days) with longer episodes up to 8 days in the first years after manifestation. They showed no constant pattern of periodicity, which is typical according to the literature.[19 21] Thus, a genetic analysis for MVK was indicated in the present case. The diagnosis of HIDS in adult patients is an exceptional finding. However, a late onset does not exclude HIDS.

We could not find a lymphadenopathy or a splenomegaly in this presentation during the symptom-free period. However, the patient reported about headache, arthralgia and myalgia during the fever episodes. These symptoms are the most frequent symptoms of HIDS patients according to case series.[19 23 24] Location of arthralgia in the knees has been frequently observed in up to 83.3% of the cases.[19]

On the basis of the clinical data of 170 cases of HIDS reported to the hyper-IgD registry in Nijmegen, the Netherlands, most of the patients are Caucasian and from Western Europe, 60% of them having a Dutch or French ancestry.[21] Our patient had no family members from France or the Netherlands.

HIDS and MA are caused by mutations of the *MVK* gene, leading to a significantly reduced residual activity (HIDS) or almost complete loss of function (MA). Some mutations resulting in severely impaired or truncated enzyme lead to MA, for example, N301T.[25] V377I, in contrast, is found only in HIDS, being the most frequent mutation.[26] It was present in 50–80% of the patients.[27–29] The next most frequent mutation of the *MVK* gene found in HIDS patients is I268T, followed by H20P.[26 27] V377I is connected with a mild phenotype, especially in the homozygous state,[16 26] but most patients are compound heterozygotes.[16] Other mutations responsible for HIDS include A148T, N205D and P165L.[13 16 28]

Until 2006, 63 *MVK* gene mutations had been published.[17] The INFEVERS autoinflammatory mutation online registry lists 204 mutations and sequence variants of the MVK gene (last accessed 13 July 2016).[30–33] Of these, 17 were exclusively found in MA, 103 in HIDS and 4 (I268T, H20P, S272F, R241C) could be found in both disease presentations. The remaining mutations did not result in a symptomatic phenotype, or they caused a not classified autoinflammatory syndrome, recurrent fever or Behcet's disease.

To the best of our knowledge, the mutation p.Gly336Ser/G336S is reported for the first time in the scientific literature,

and our patient is only the second individual known to carry this mutation. The other case was a symptomatic Italian patient submitted to the registry on 2006-05-02 by Andrea D'Osualdo and Isabella Ceccherini.[30]

The p.Gly336Ser mutation is very likely responsible for the fever episodes due to structure-function considerations based on the structure of the enzyme mevalonate kinase published in 2002,[34] and an analysis with the programme PolyPhen-2, giving a severity score of 1.0. The amino acid exchange is located within the fourth conserved region consisting of the amino acids 329–344, the glycine at position 336 being part of a tight glycine-rich loop (Motif 3) conserved in several organisms.[28 34] In close proximity of this glycine, another amino acid substitution has been discovered in 1997: a conserved alanine at position 334 is replaced by threonine (p.Ala334Thr or A334T). The mutant enzyme showed a reduced binding affinity to mevalonate.[35] This is the consequence of a steric hindrance in the binding site, the enzyme activity being only about 1.4% of the wild type.[35] It was speculated that this region could provide a hydrophobic environment to stabilise also hydrophobic mevalonate and act as the active side of the enzyme.[35] With optimal shielding of mevalonate against the solvent, the enzyme activity raises. The tight turn (residues 331-339 LTGAGGGGC) may be important for this shielding of the substrate. Moreover, a sequence variant resulting in a replacement of the adjacent glycine at position 335 by alanine (p.Gly335Ala or G335A) has been contributed to the INFEVERS registry, but functional information is not available.[30] Related enzymes with a similar motif such as the phosphomevalonate kinase from *Saccharomyces cerevisiae* and the homoserine kinase from *Methanocaldococcus jannaschii* have a glycine-alanine-glycine and glycine-serine-glycine sequence, respectively, instead of three glycines. Therefore, replacement of the glycine at position 336 does not totally disrupt the structure.[34]

As our patient was tested compound heterozygous for p.Val377Ile/V377I, it is not possible to comment on the phenotypical consequences of the newly described mutation G336S. But we suppose that the mutation results in a mild phenotype. Compound heterozygous V377I carriers usually exhibit a mild phenotype even when accompanied by a mutation leading to a more severe loss of MVK activity. In contrast to our patient, the ensuing phenotype is usually clinically present in early childhood. In general, in the compound heterozygous state the mutation leading to the more active enzyme variant is determining the residual activity and thereby the phenotype.

Learning points

- Hereditary autoinflammatory syndromes are a very heterogeneous group of diseases with a wide range of clinical presentations. Pathophysiologically, they are still incompletely understood.
- The diagnosis of a hereditary autoinflammatory syndrome can be missed even in cases with a long history of FUO.
- New mutations could explain unusual presentations.

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Contributors JKR took care for the patient and initiated the case report. The case and the clinical background were discussed with CS-Z and PL. CS-Z made substantial discussions and proofreading. SS wrote the draft together with JKR. The genetic background was discussed by PL. All four authors approved the final version. JKR and SS take responsibility for the case report as a whole. SS takes responsibility for journal style and formal issues.

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