Pediatric rheumatology review

Mevalonate kinase deficiency and Dutch type periodic fever

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ABSTRACT

Dutch type periodic fever (DPF) is an autosomal recessive hereditary fever syndrome. Cases have been reported worldwide, the majority from France and The Netherlands. From infancy the patients suffer fever attacks that recur every 2-8 weeks, often precipitated by immunizations, infections or emotional stress. Fever lasts 2-7 days and can be accompanied by malaise, headache, diarrhea, abdominal pain, vomiting, skin rashes, arthralgia, arthritis, tender lymphadenopathy, hepatosplenomegaly, and oral and genital ulcers. Labarotory evaluation during fever shows granulocytosis and elevated acute phase reactants.

DPF is caused by a deficiency of the enzyme mevalonate kinase (MK). Besides DPF, the spectrum of MK deficiency includes a severe phenotype, mevalonic aciduria (MA). MA patients have less residual MK activity, leading to substantially higher urinary mevalonic acid excretion than in DPF. Mevalonic aciduria is characterized by mental retardation and dysmorphic features in addition to the clinical features of DPF. At the genomic level, several mutations of varying severity have been identified. The DPF phenotype is caused by one particular mild missense mutation. Most patients are compound heterozygotes for this mutation and a more severe mutation.

The mechanism by which MK deficiency leads to fever is not understood. The vast majority of DPF patients have persistently elevated serum IgD and can be classified as having hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). Conversely, most HIDS patients have MK deficiency and hence DPF, but the two disorders do not overlap entirely.

Introduction

The first reports of of children with recurrent febrile attacks in the presence of an abnormally high serum IgD concentration were published in 1984 (1). The first detailed description of this disorder, was published by van der Meer *et al.* (2), who introduced the term hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). Most patients have been of Dutch extraction, although cases have been reported worldwide (3). Hence, the disease is also known as Dutch type periodic fever (DPF, MIM#260920).

Inheritance is autosomal recessive. The first febrile crises usually occur in infancy and recur at varying intervals. The crises are typically triggered by infections and childhood immunizations. In addition to fever the patients often experience malaise, chills, headache, arthralgias, nausea, abdominal pain, and diarrhea, and show cutaneous rashes, hepatosplenomegaly, tender cervical lymphadenopathy, and frank arthritis (3). Granulocytosis and elevated acute phase reactants during attacks are indicative of an acute inflammatory reaction, but a satisfactory explanation for these findings is lacking. Linkage analysis excluded the gene affected in FMF as a candidate involved in the etiology of HIDS (4).

The cause of HIDS remained obscure until 1999. Then, HIDS patients were shown to have mutations in the gene *MVK*, which codes for the enzyme mevalonate kinase (MK, EC. 2.7.1.36) (5, 6). MK is an early enzyme in isoprenoid biosynthesis (Fig. 1). This biochemical pathway produces several compounds, including cholesterol. Deficient MK enzyme activity had been described previously in a rare autosomal recessive disease, mevalonic aciduria (MA, MIM# 251170) (7). MA is characterized by mild to severe mental retardation, cerebellar atrophy, manifested by progressive ataxia and dysarthria, myopathy, leading to hypotonia, and cataracts. Most of these children have dysmorphic facial features.

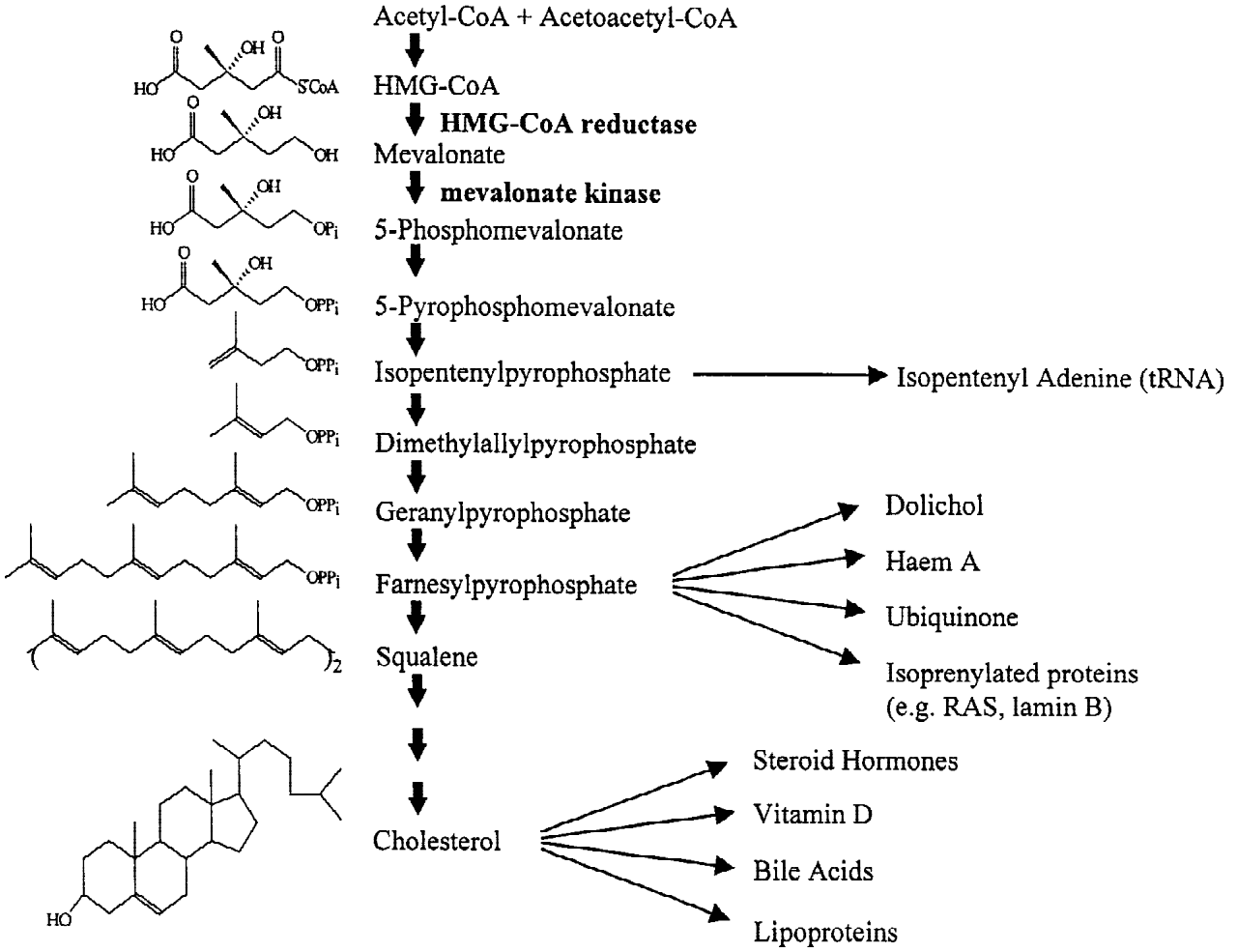

Fig. 1. Isoprenoid biosynthesis. Mevalonate kinase catalyzes the reaction immediately after HMG-CoA reductase. End products of this route include isopentenyl tRNAs, dolichol, Heme A, ubiquinone, farnesyl and geranylgeranyl groups for protein isoprenylation, and cholesterol, with all its derivatives. In mevalonate kinase deficiency there is accumulation of mevalonic acid.

Interestingly, MA patients suffer frequent inflammatory attacks, with fever, vomiting, diarrhea, arthralgias, cervical lymphadenopathy and hepatosplenomegaly, during which white blood cell counts and acute phase reactants are elevated (8). Hence, despite the differences between MA and HIDS, the inflammatory crises are similar. The attacks are caused in some way by the MK deficiency, but it is not yet understood how. Not all patients with periodic fever and elevated IgD have MK deficiency. Most of what we know about DPF dates from before the identification of the molecular defect. Here we will use the term DPF for those patients who suffer recurrent febrile attacks and have reduced MK activity. The term HIDS then includes all patients with periodic fever and hyper IgD not explained by infectious or immunological diseases, irrespective of MK activity.

Epidemiology

At least 144 patients have been diagnosed with HIDS worldwide (9). Most of these are from Europe, the majority being Dutch (55%) and French (25%), with far smaller numbers being reported from Sweden, Germany, the Czech Republic, the United Kingdom, Belgium, Italy, and Spain. Patients have also been reported from Turkey (10), Japan (11) and the United States (12). Heightened awareness of the disorder in France and The Netherlands may partially account for the higher numbers of patients reported from these countries as compared to neighboring states like Belgium and Germany.

Though the exact incidence of HIDS is unknown, its prevalence in the Netherlands is estimated to be 5 or 6 cases per million total population. In reality, this figure is probably higher.

Symptoms

Disease onset in HIDS is, characteristically, in infancy. Subsequently, patients suffer repeated attacks, which can be precipitated by infections, minor trauma, physical or emotional stress, menses, and by childhood immunizations. Most attacks, however, occur without any clear precipitating event (3). The duration of the fever attacks can vary between patients and even from attack to attack in the same patient. In general, fever lasts for 2 to 7 days, more commonly 3 to 4 days. However, after the normalization of body temperature, it may take several days to weeks before general wellbeing is restored. Some patients with frequent febrile attacks do not recover entirely in-between. The episodes typically recur without strict periodicity, once every 3 to 6 weeks. However, patients may experience attacks from once every two

Table I. Cumulative incidence of symptoms and signs during febrile attacks in HIDS (modified from reference 3).

Fever	100%	Lymphadenopathy	94%
Chills	76%	Skin rash	82%
Abdominal pain	72%	Splenomegaly	48%
Diarrhea	82%	Serositis	6%
Vomiting	56%	Arthritis	68%
Headache	52%		
Arthralgias	80%		

weeks to once every 2 years. As patients grow older, attacks tend to become less severe and less frequent and there may even be prolonged disease-free intervals. Fever is the dominant feature of the attacks. Body temperature rises abruptly, often with chills or rigors, remains high, often over 40°C, and then gradually returns to normal. Immediately preceding the attacks many patients experience malaise, headache, a sore throat or nasal congestion; in children irritability and hyperactivity are often noted.

During the febrile attacks the patients may have various other symptoms (Table I). Abdominal pain, diarrhea and vomiting are common. The pain is sometimes sufficiently severe to be confused with that of acute appendicitis. Non-bloody diarrhea is prominent in young children. Arthralgias accompany fever in most cases. Frank arthritis, mostly affecting the large joints of the lower extremities, is also common and may persist between crises. Patients frequently complain of severe headaches (3).

Signs

Tender cervical lymphadenopathy is a constant finding during febrile attacks (3) and the axillary, inguinal and intra-abdominal lymph nodes may also be swollen.

Splenomegaly is present in nearly half of the patients, though it is a rare finding in adult patients, whereas hepatomegaly is almost exclusively seen in pediatric patients.

Rashes have been observed in most HIDS cases. These may be macular, maculopapular, urticarial, nodular or, rarely, purpuric (13). One Japanese patient has been reported with erythema elevatum diutinum (11). Oral and genital ulcers occur frequently in HIDS (14) and in one patient rectal ulcers have been observed (15). Serositis is not a regular feature of HIDS. However, acute intestinal obstruction due to adhesions has been described in 3 patients, 2 of whom had had no prior surgery (3).

Laboratory findings

Blood abnormalities during attacks are indicative of an acute phase response. Leukocytosis and granulocytosis are consistent findings; furthermore, the erythrocyte sedimentation rate and C reactive protein concentration are strongly elevated. In between attacks these values return to normal (16). Complement levels (C3, C4, CH_{50}) are normal or raised with no indication of an increased consumption of complement, whereas circulating immune complexes are present at low levels in 20% of patients (3). About 16% of patients have microscopic hematuria during attacks, but impairment of renal function is very rare (17).

Immunological findings

IgD

IgD is a heavily glycosylated immunoglobulin. It comes in two forms, membrane bound and secreted. Its physiological role is largely unknown, as is its role in the pathogenesis of HIDS. Normally serum IgD concentrations are below 100 IU/ml, but they can rise during infectious and non-infectious inflammatory diseases (18-20). Polyclonal elevation of serum IgD is a prerequisite for the diagnosis of HIDS. Hence, all patients reported have had raised serum IgD at some point in their disease course. There is, however, no relationship between disease activity and the IgD concentration (2). IgD can even be entirely normal at times, despite patients having active disease. In young children symptoms can exist for as long as 3 years before there is any rise in serum IgD (21). With the identification of MK deficiency, it has become possible to recognize DPF in patients with persistently normal IgD levels. Only one such patient has been described, but this shows that increased IgD levels are not a prerequisite for the diagnosis of DPF (5).

The high serum IgD level is more likely to be an epiphenomenon than a cause of the inflammatory state in HIDS, despite indications that IgD may stimulate cytokine secretion *in vitro* (22). Furthermore, elevated IgD is not unique for HIDS since it has been described in patients with other inflammatory conditions, notably the periodic fever aphtous stomatitis pharyngitis adenitis syndrome (20), familial Mediterranean fever (18), Behçet's disease (23), bronchiectasis, and immunodeficiency disorders (19), but it is not a consistent finding in any of these disorders.

The high serum IgD concentration in HIDS is due to increased production, as evidenced by the high numbers of IgD-containing plasma cells (2) in bone marrow aspirates (21). The mechanism that leads to this increased synthesis of IgD in HIDS is unknown.

Other immunoglobulins

Other immunoglobulins are freqently elevated as well. IgA is raised in up to 82% of HIDS patients. Serum IgM can be high as well, but may be normal or even low. Similarily, serum IgG is usually normal but may be raised, predominantly due to elevated IgG3 levels.

Cytokines

Cytokine production in HIDS has been studied both *in vivo* and *in vitro*, with attention focused on cytokines, known to induce fever and on mediators with antiinflammatory properties. These measurements have been performed in plasma and in supernatants of cultured leukocytes from HIDS patients. During febrile attacks the serum levels of interferon-γ, and interleukin (IL)-6 rise sharply (24, 25), and tumor necrosis factor (TNF)-α rises to high normal values, whereas IL-1α and IL-1β are not elevated (25). The effect of the increased stimulation of mononuclear phagocytes by interferon-γ is reflected in a rise in urinary neopterin excretion simultane-

ously with the onset of fever. The neopterin excretion remains high for several days after normalization of the body temperature (24). Serum levels of the anti-inflammatory mediators IL-1 receptor antagonist, soluble TNF receptor p55 and soluble TNF receptor p75 are raised during attacks, whereas IL-10 remains normal (25).

The production of many of these mediators has been studied *in vitro*. In supernatants of unstimulated cultures of whole blood samples, obtained during attacks, IL-1β is not increased (25). Culture supernatants of peripheral blood mononuclear cells (MNC) obtained between attacks, however, contained high concentrations of IL-1 β which increased even further upon stimulation with LPS (26). Although plasma levels of TNF-α stay within normal limits, its concentration is increased in the supernatants of unstimulated cultures of whole blood samples drawn between attacks. When stimulated with LPS the supernatants of such cultures showed an elevated TNF-α level, which was even higher when the blood cells had been obtained during an attack (25). Similar results were obtained in culture supernatants of isolated MNC obtained between attacks (26).

Taken together these data are compatible with macrophage activation during the febrile attacks. Between the febrile attacks the *in vitro* findings are still compatible with an increased activity of the mononuclear phagocytic compartment. The cause of this macrophage activation is unknown. While activated T_{helper}-1 cells are known to induce macrophage activation, the high IgD and IgA levels are more compatible with an increased activity of T_{helper}-2 cells (27). However, direct evidence of T-cell activation during attacks is lacking.

Biochemistry

The identification of MK deficiency as the cause of DPF links this syndrome to mevalonic aciduria. This latter inborn error was first described by Berger *et al.* in 1985 (28) and subsequently recognized to be caused by a deficiency of MK enzyme activity (29). In MA the MK enzyme activity is usually virtually absent when measured in cultured skin fibroblasts or lymphoblasts of patients (0 to 4% of the control mean) (8, 30). In DPF, however, a residual MK activity varying between 1 and 7% can be measured both in fibroblasts and leukocytes from patients (5). As a result of the MK deficiency, excretion of mevalonic acid in urine occurs, although the levels of excreted mevalonic acid vary significantly between both syndromes. MA is characterized by a massive and constitutive excretion (1000-56000 mmol/mol creatinine) (8), while in DPF the mevalonic acid excretion is moderate (4-28 mmol/mol creatinine) and may be normal between febrile crises (5). In healthy controls, the excretion of mevalonic acid in urine is usually less than 1 mmol/mol creatinine.

MK is the first enzyme to follow 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) in the mevalonate pathway and converts mevalonate into 5-phosphomevalonate (Fig. 1). The mevalonate pathway provides cells with isoprenoids that are essential for diverse cellular processes. The main end products include ubiquinone-10 and haem A, both of which are necessary for electron transport, isopentenyl tRNA (involved in protein translation), dolichol (essential for N-linked protein glycosylation), and the farnesyl and geranylgeranyl groups used for isoprenylation of the proteins involved in cell proliferation and differentiation. In addition to these non-sterol isoprenoids the mevalonate pathway produces cholesterol, a structural component of cellular membranes and precursor for bile acids and steroid hormones (31).

HMG-CoA reductase, which converts HMG-CoA into mevalonate, catalyzes the main rate-limiting step in isoprenoid biosynthesis and is among the most tightly regulated enzymes in nature (31). Indeed the statins, which are drugs widely used to treat atherosclerosis and familial hypercholesterolaemia, are potent competitive inhibitors of the reductase; they block the synthesis of mevalonate and as a consequence lower the endogenous synthesis of cholesterol. The use of statins can trigger adaptive reactions yielding up to 200-fold increased HMG-CoA reductase activity. A therapeutic trial in which two MA patients were treated with low doses of lovastatin in order to block mevalonate production, however, was unsuccessful and had to be abandoned because of the development of severe clinical crises.

Currently, five metabolic diseases have been described which are caused by defects in the mevalonate pathway. Three disorders, Smith-Lemli-Opitz syndrome (32-34), desmosterolosis (35), and X-linked dominant chondrodysplasia punctata (36, 37) only affect the sterol biosynthesis. MA and DPF affect the biosynthesis of all isoprenoids. Periodic fevers and dysregulation of the immune system are only present in DPF and MA, which indicate that a shortage of cholesterol is not the pathogenetic basis of the periodic fevers. This is also supported by the observation that cholesterol levels are usually (near) normal in patients with MA (8). Furthermore, the incorporation of radiolabeled acetyl-CoA into cholesterol by cultured skin fibroblasts of DPF and MA patients appears to be comparable with that in controls (38).

The differences in mevalonate excretion between DPF and MA could be caused by a difference in the regulation of HMG-CoA reductase activity. In MA there may be a constitutive derepression of HMG-CoA reductase, as suggested by the elevated reductase activity in fibroblasts from MA patients (38) and the levels of excreted mevalonate (> 800 mmol/day) which greatly exceed the level of normal whole body cholestrol biosynthesis (4 mmol/day, equivalent to 24 mmol of mevalonate/day) (8), while in DPF the reductase activity may only be derepressed during fever episodes. Studies to investigate this in further detail are underway.

Molecular biology

The cause of DPF was independently identified in 1999 by a Dutch research group and Dutch/French consortium using two different approaches. Both groups ended up with the same gene, *MVK*, coding for the enzyme MK. Houten *et al.* (5) performed organic acid analysis of urine from one periodic fever patient during an episode of fever and found elevated levels of mevalonic acid. This patient had all the characteristics of HIDS except for an elevated IgD. Subsequent organic acid analysis in 2 HIDS patients,

however, also revealed elevated levels of mevalonic acid during episodes of fever. The elevated levels of mevalonic acid in urine suggested a defect in the metabolism of mevalonate, and enzyme measurements revealed a profound deficiency of MK enzyme activity.

Subsequent mutation analysis revealed several disease-causing mutations in the *MVK* gene. Drenth *et al.* performed linkage analysis and obtained linkage at chromosome 12 position q24 (6). After narrowing the region to 9 cM, they concluded that *MVK* was a good candidate gene and subsequently identified mutations in this gene in several HIDS patients. Since the human MVK cDNA sequence had already been cloned, both groups performed mutation analysis at the cDNA level. This revealed a common missense mutation, a G > A transition at nucleotide 1129 changing the valine at position 377 into a isoleucine (V377I) (5, 6), in 20 out of 21 HIDS patients (39). Most patients were compound heterozygotes for this mutation. Two additional missense mutation were identified, an A > C transversion at nucleotide 59 and a T > C transition at nucleotide 803, which change the histidine at position 20 into a proline (H20P) and the isoleucine at position 268 into a threonine (I268T), respectively. Since the latter two mutations were also identified in MA patients (30, 40), this strongly suggested that the V377I mutation is responsible for the DPF phenotype of MK deficiency. Indeed, thus far only one patient has been described without this mutation (6). This patient was compound heterozygous for a C > T transition at nucleotide 500, changing the proline at position 165 into a leucine (P165L). The other allele carried the I268T mutation, which was also found in MA patients, suggesting that the P165L mutation is responsible for the DPF phenotype in this patient.

The *MVK* gene was previously reported to be a single copy gene located on chromosome 12 postion q24 (41, 42), which is in accordance with the linkage analysis performed by Drenth *et al*. (6). We have recently resolved the genomic organization of the mevalonate kinase gene, showing it to consist of 11 exons (unpublished data). Figure 2 is a schematic representation of the *MVK* gene and includes all the mutations currently identified in both MA and Dutch type periodic fever.

In order to study the effect of the identified missense mutations on MK activity, most of the mutant proteins have been characterized by immunoblotting and heterologous expression. The first identified mutation in MA, N301T, was expressed in COS-7 cells and showed a markedly decreased enzyme activity varying between 5 and 20% of the activity of wild type MK 41). More recently, a mutation in MA was characterized, which changed the affinity of the enzyme for its substrate mevalonate when expressed as a recombinant fusion protein in *Escherichia coli* (A334T) (43). The V377I mutation had considerable residual activity when expressed in *E. coli* (35% compared to the control), but MK protein in fibroblast lysates of HIDS patients was hardly detectable, as shown by immunoblotting with an MK-specific antibody. This indicates that, although this mutation has some effect on enzyme activity, it predominantly affects the stability of the MK protein *in vivo* (5). All of the other characterized mutations result in MK proteins with markedly decreased enzyme activity when expressed in *E. coli* and/or decreased protein levels in fibroblast lysates (H20P, T243I, L264F, L265P, I268T and V310M) (30, 40).

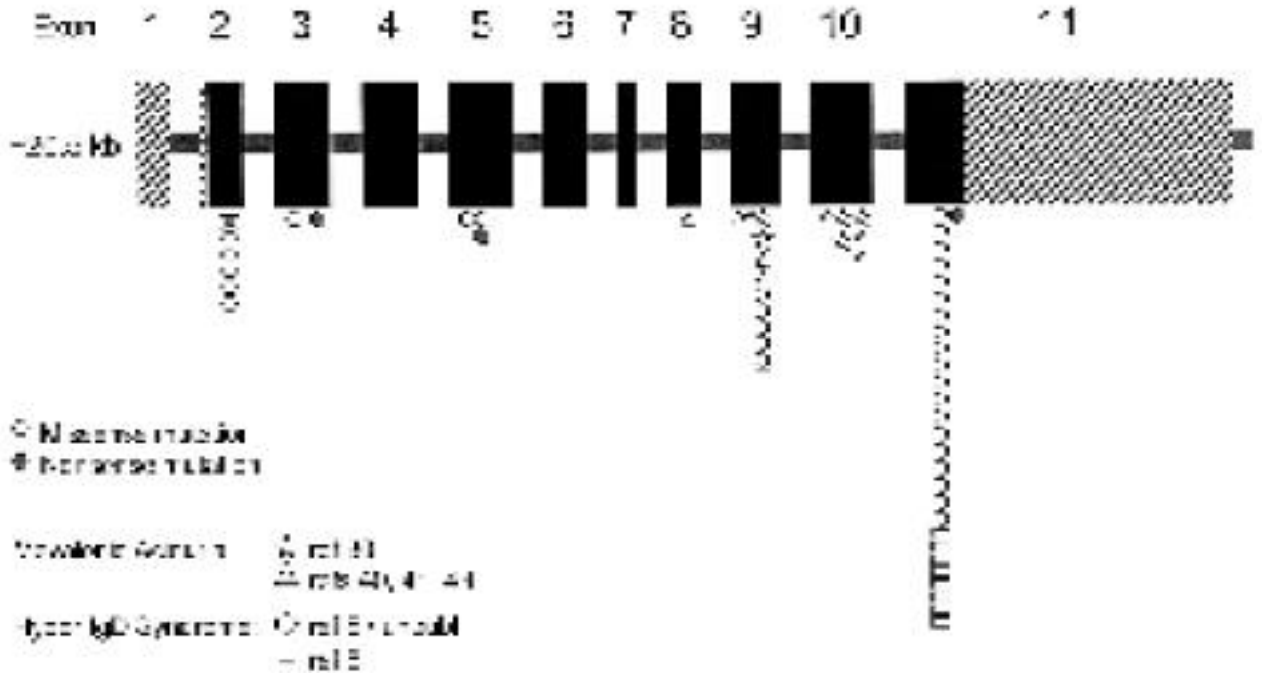

Fig. 2. Schematic representation of the organization of the *MVK* gene. The locations of all the mutations identified at present in Dutch type periodic fever and mevalonic aciduria are indicated.

Differential diagnosis

DPF should be distinguished from a number of hereditary and non-hereditary disorders with which it has features in common. First, infectious diseases and cyclic neutropenia should be ruled out.

Systemic onset juvenile chronic arthritis, like DPF, is characterized by fevers, transient rashes, lymphadenopathy, hepatosplenomegaly, and arthritis. However, the onset is rarely in the first year of life, the fever has a spiking pattern, the disease flares usually last many weeks instead of days, and the arthritis is destructive. Contrary to DPF, serositis is common and diarrhea is usually absent. Furthermore, there is no ethnic predisposition and the disease is not familial in occurrence.

Familial Mediterranean fever typically occurs in patients of Turkish, Armenian, Iraqi or Sephardic Jewish ancestry. It is characterized by recurrent bouts of high fever, accompanied by arthritis and by severe abdominal pain due to serositis. Patients may have pleuritis, pericarditis or an erysipeloid rash of the lower part of the legs. The onset of attacks is usually at a later age (2-10 years) than in HIDS and the attacks typically last only 12-72 hours (44). Diarrhea, headache, generalized rashes, lymphadenopathy and hepatosplenomegaly do not feature in FMF. Amyloidosis is a common serious late complication of FMF, which may lead to nephrotic syndrome and renal failure. In contrast to DPF, the attacks of FMF can be prevented by colchicine. This treatment reduces the future development of amyloidosis. Inheritance is autosomal recessive and the responsible gene, *MEFV*, on chromosome 16p13.3 codes for a protein of unknown function called pyrin or marenostrin (45,46). Molecular diagnosis is feasible in most FMF patients, but in at least 20% of patients one or both alleles appear normal (44, 47, 48).

The TNF-receptor associated periodic syndrome (TRAPS) is a rare disorder that has been encountered primarily in Irish and British families and was therefore called familial hibernian fever, but it has also been encountered in families from other countries, including France and The Netherlands. The onset of this disease is between 2 and 20 years of age, after which febrile attacks recur at irregular intervals, typically 2 to 4 times every year (49). The duration of fever varies from some days to many weeks. The fever may be accompanied by conjunctivitis, myalgias, painful erythema of the arms and legs, arthralgias, and scrotal and abdominal pain. As in FMF, these patients may have serositis, and some have developed amyloidosis. In contrast to DPF, lymphadenopathy is absent. Inheritance is autosomal dominant and molecular diagnosis has become possible with the identification of the affected gene, *TNFR1*. This gene encodes the 55 kDa TNF receptor protein (50) and mutations affect the extracellular domain of this receptor, interfering with receptor shedding.

The periodic fever known as aphtous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome is characterized by febrile attacks that last 2-8 days and recur every 2-8 weeks. The fever is accompanied by aphtous stomatitis, cervical lymphadenopathy and pharyngitis, but some patients also experience headache, abdominal pain, diarrhea or rashes. IgD may be mildly elevated. Hence, differentiation from HIDS can be particularly difficult. The PFAPA syndrome is, however, not familial in occurrence (20, 51).

Although the majority of patients initially classified as HIDS were MK deficient when tested, some patients were found to have normal MK activity. These children tend to have a later age of disease onset, but could not otherwise be distinguished from DPF cases.

Ultimately, the correct diagnosis of DPF can only be made by the demonstration of a reduced MK activity in cultured skin fibroblasts or mononuclear cells

A simplified flow diagram of the diagnostic approach in children with recurrent fever is shown in Figure 3.

Treatment

No systematic study of therapeutic interventions in HIDS has been reported. Non-steroidal anti-inflammatory drugs, colchicine, intravenous immunoglobulins, and cyclosporin A have been tried in some patients and were, in most cases, found to be ineffective. Some patients responded favorably to corticosteroids. The long-term use of corticosteroids in childhood has too many side effects, however, to justify their use as maintenance treatment to prevent attacks.

Prognosis

The frequency and the severity of attacks appear to decrease with age. In our experience, however, all children with DPF have remained symptomatic. In contrast, children with recurrent fever and elevated serum IgD but normal MK activity were likely to enter long-term remission. There are some indications that pregnancy may further decrease disease activity (52). Some patients have long-term sequelae, however. Three patients developed peritoneal adhesions, possibly as a consequence of serositis. Amyloidosis was described in one patient (3) and one child developed end stage renal failure due to crescentic glomerulonephritis (17). Joint damage has not been reported in HIDS.

Among the patients in the HIDS registry two deaths have been reported, one by suicide and one from a stroke (3). It is doubtful whether these complications are related to HIDS.

Though HIDS may cause little excess mortality or permanent organ damage, the impact of a disease that causes patients to miss school frequently from kindergarden through high school cannot be underestimated. Data on the psychosocial effects are lacking, however.

Future directions

The identification of the molecular defect in DPF will have implications for our understanding of the disease, its pathogenesis, its natural history and its treatment. Efforts are underway to elucidate the pathophysiological mechanisms by which mevalonate kinase deficiency leads to periodic fever. Other defects in the isoprenoid pathway with similar clinical effects might be expected, but these have not yet been identified.

With a definitive diagnostic criterion at hand, the patient population is better defined, which will enable us to reappraise the clinical presentation and the natural course of the disease.

Finally, we are now in a position to assess prospectively the effect of interventions in a circumscript patient group. The

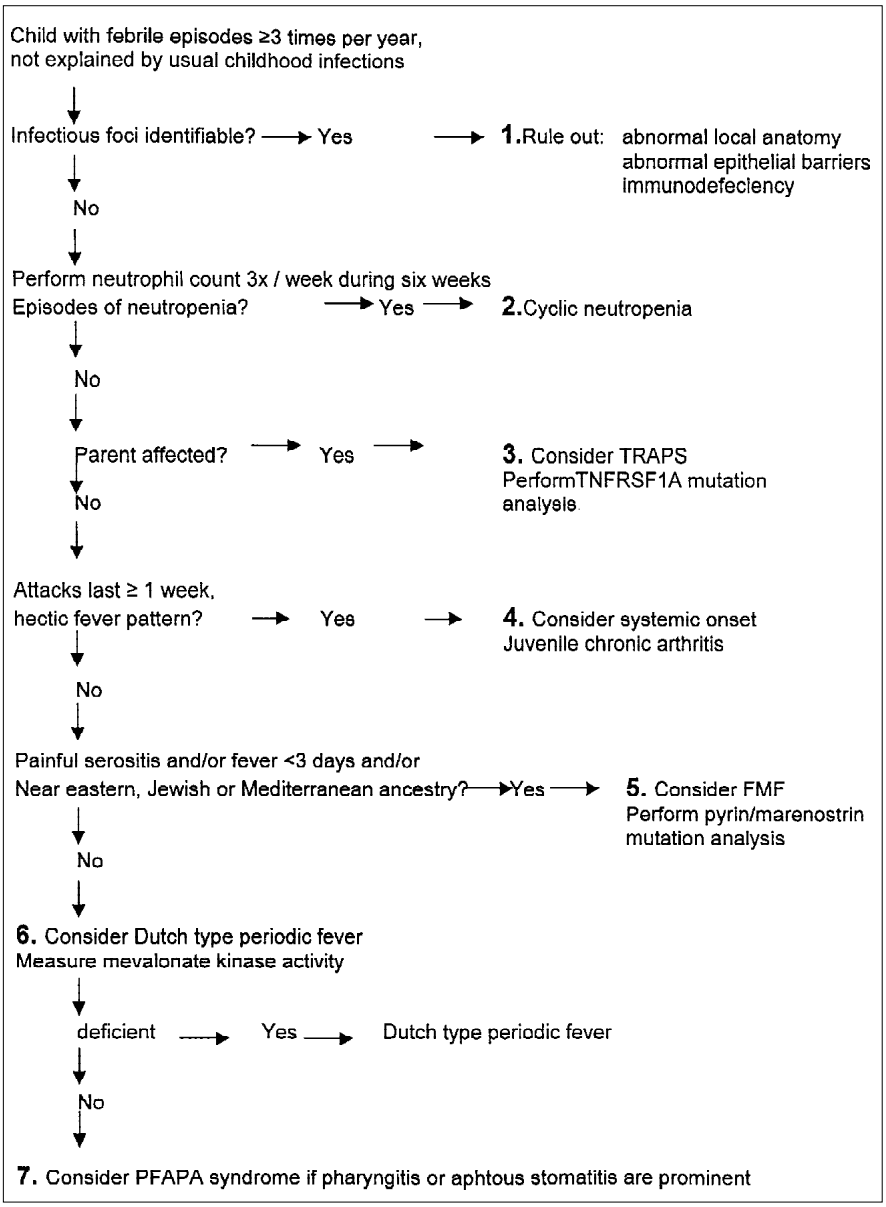

Fig. 3. Diagnostic approach to recurrent fever in childhood.

involvement of the isoprenoid pathway in the pathogenesis suggests that treatment with statins, which interfere in the earliest step of this route, might be beneficial. A clinical trial with such a compound is to start soon (9).

Results of both mechanistic studies and intervention trials should ultimately shed light on the physiological role of isoprenoid metabolism in inflammation.

References

1. PRIEUR AM, GRISCELLI C: Aspect nosologique des formes systemiques d'arthrite juvenile a debut tres precoce. A propos de dix-sept observations. *Semin Hôp* 1984; 60: 163-7.
2. VAN DER MEER JW, VOSSEN JM, RADL J *et al.*: Hyperimmunoglobulinaemia D and periodic fever: A new syndrome. *Lancet* 1984; 1: 1087-90.
3. DRENTH JP, HAAGSMA CJ, VAN DER MEER JW: Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. International Hyper-IgD Study Group. *Medicine (Baltimore)* 1994; 73: 133-44.
4. DRENTH JP, MARIMAN EC, VAN DER VELDE-VISSER SD, ROPERS HH, VAN DER MEER JW: Location of the gene causing hyperimmunoglobulinemia D and periodic fever syndrome differs from that for familial Mediterranean fever. International Hyper-IgD Study Group. *Hum Genet* 1994; 94: 616-20.
5. HOUTEN SM, KUIS W, DURAN M *et al.*: Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. *Nat Genet* 1999; 22: 175-7.
6. DRENTH JP, CUISSET L, GRATEAU G *et al.*: Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. *Nat Genet* 1999; 22: 178-81.
7. HOFFMANN G, GIBSON KM, NYHAN WL, SWEETMAN L: Mevalonic aciduria: Pathobiochemical effects of mevalonate kinase deficiency on cholesterol metabolism in intact fibroblasts. *J Inherit Metab Dis* 1988; 11 (Suppl. 2): 229-32.
8. HOFFMANN GF, CHARPENTIER C, MAYATEPEK E *et al.*: Clinical and biochemical phenotype in 11 patients with mevalonic aciduria. *Pediatrics* 1993; 91: 915-21.
9. SIMON A, DRENTH JP: Genes associated with periodic fevers highlighted at Dutch workshop. *Lancet* 1999; 354: 2139.
10. TOPALOGLU R, SAATCI U: Hyperimmunoglobulinaemia D and periodic fever mimicking familial Mediterranean fever in the Mediterranean. *Postgrad Med J* 1991; 67: 490-1.
11. MIYAGAWA S, KITAMURA W, MORITA K, SAISHIN M, SHIRAI T: Association of hyperimmunoglobulinaemia D syndrome with erythema elevatum diutinum. *Br J Dermatol* 1993; 128: 572-4.
12. GROSE C, SCHNETZER JR, FERRANTE A, VLADUTIU AO: Children with hyperimmunoglobulinemia D and periodic fever syndrome. *Pediatr Infect Dis J* 1996; 15:72-7.
13. DRENTH JP, BOOM BW, TOONSTRA J, VAN DER MEER JW: Cutaneous manifestations and histologic findings in the hyperimmunoglobulinemia D syndrome. International Hyper IgD Study Group. *Arch Dermatol* 1994; 130: 59-65.
14. GROUTEAU E, CHAIX Y, GRABER D *et al*: Pseudomaladie periodique avec hyperimmunoglobulinemie D: Une histoire sans fin de debut antenatal probable. *Arch Pediatr* 1998; 5: 280-4.
15. OZIOL E, RIVIERE S, LE QUELLEC A, CIURANA AJ: La fievre qui venait du nord. *Rev Med Interne* 1999; 20 (Suppl. 2): 236s-8s.
16. HAVENAAR EC, DRENTH JP, VAN OMMEN EC, VAN DER MEER JW, VAN DIJK W: Elevated serum level and altered glycosylation of alpha 1-acid glycoprotein in hyperimmunoglobulinemia D and periodic fever syndrome: Evidence for persistent inflammation. *Clin Immunol Immunopathol* 1995; 76: 279-84.
17. TSIMARATOS M, KONE-PAUT I, DANIEL L, GUBLER MC, DUSSOL B, PICON G: Crescentic glomerulonephritis in hyper IgD syndrome. *Pediatr Nephrol* 1999; 13: 132-4.
18. LIVNEH A, DRENTH JP, KLASEN IS *et al.*: Familial Mediterranean fever and hyperimmunoglobulinemia D syndrome: Two diseases with distinct clinical, serologic, and genetic features. *J Rheumatol* 1997; 24: 1558-63.
19. HIEMSTRA I, VOSSEN JM, VAN DER MEER JW, WEEMAES CM, OUT TA, ZEGERS BJ: Clinical and immunological studies in patients with an increased serum IgD level. *J Clin Immunol* 1989; 9: 393-400.
20. PADEH S, BREZNIAK N, ZEMER D *et al.*: Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: Clinical characteristics and outcome. *JPediatr*1999;135:98-101.

21. HARALDSSON A, WEEMAES CM, DE BOER AW, BAKKEREN JA, STOELINGA GB: Immunological studies in the hyper-immunoglobulin D syndrome. *J Clin Immunol* 1992; 12: 424-8.
22. DRENTH JP, GOERTZ J, DAHA MR, VAN DER MEER JW: Immunoglobulin D enhances the release of tumor necrosis factor-alpha, and interleukin-1 beta as well as interleukin-1 receptor antagonist from human mononuclear cells. *Immunology* 1996; 88:355-62.
23. SAKANE T, TAKENO M, SUZUKI N, INABA G: Behçet's disease. *N Engl J Med* 1999; 341: 1284-91.
24. DRENTH JP, POWELL RJ, BROWN NS, VAN DER MEER JW: Interferon-gamma and urine neopterin in attacks of the hyperimmunoglobulinaemia D and periodic fever syndrome. *Eur J Clin Invest* 1995; 25: 683-6.
25. DRENTH JP, VAN DEUREN M, VAN DER VEN-JONGEKRIJG J, SCHALKWIJK CG, VAN DER MEER JW: Cytokine activation during attacks of the hyperimmunoglobulinemia D and periodic fever syndrome. *Blood* 1995; 85: 3586-93.
26. DRENTH JP, VAN DER MEER JW, KUSHNER I: Unstimulated peripheral blood mononuclear cells from patients with the hyper-IgD syndrome produce cytokines capable of potent induction of C- reactive protein and serum amyloid A in Hep3B cells. *J Immunol* 1996; 157: 400-4.
27. LEVAN-PETIT I, LELIEVRE E, BARRA A *et al.*: T(h)2 cytokine dependence of IgD production by normal human B cells. *Int Immunol* 1999; 11: 1819-28.
28. BERGER R, SMIT GP, SCHIERBEEK H, BIJSTERVELD K, LE COULTRE R: Mevalonic aciduria: An inborn error of cholesterol biosynthesis ? *Clin Chim Acta* 1985; 152: 219-22.
29. HOFFMANN G, GIBSON KM, BRANDT IK, BADER PI, WAPPNER RS, SWEETMAN L: Mevalonic aciduria - an inborn error of cholesterol and nonsterol isoprene biosynthesis. *N Engl J Med* 1986; 314: 1610-4.
30. HOUTEN SM, ROMEIJN GJ, KOSTER J *et al.*: Identification and characterization of three novel missense mutations in mevalonate kinase cDNA causing mevalonic aciduria, a disorder of isoprene biosynthesis. *Hum Mol Genet* 1999; 8:1523-8.
31. GOLDSTEIN JL, BROWN MS: Regulation of the mevalonate pathway. *Nature* 1990; 343: 425-30.
32. FITZKY BU, WITSCH-BAUMGARTNER M, ERDEL M *et al.*: Mutations in the Delta7-sterol reductase gene in patients with the Smith-Lemli-Opitz syndrome. *Proc Natl Acad Sci USA* 1998; 95: 8181-6.
33. WASSIF CA, MASLEN C, KACHILELE-LINJEWILE S *et al.*: Mutations in the human sterol delta7-reductase gene at 11q12-13 cause Smith-Lemli-Opitz syndrome. *Am J Hum Genet* 1998; 63: 55-62.
34. WATERHAM HR, WIJBURG FA, HENNEKAM RC *et al.*: Smith-Lemli-Opitz syndrome is caused by mutations in the 7- dehydrocholesterol reductase gene. *Am J Hum Genet* 1998; 63: 329-38.
35. FITZPATRICK DR, KEELING JW, EVANS MJ *et al.*: Clinical phenotype of desmosterolosis. *Am J Med Genet* 1998; 75: 145-52.
36. DERRY JM, GORMALLY E, MEANS GD *et al.*: Mutations in a delta 8-delta 7 sterol isomerase in the tattered mouse and X-linked dominant chondrodysplasia punctata. *Nat Genet* 1999; 22: 286-90.
37. BRAVERMAN N, LIN P, MOEBIUS FF *et al.*: Mutations in the gene encoding 3 beta-hydroxysteroid-delta 8, delta 7- isomerase cause X-linked dominant Conradi-Hunermann syndrome. *Nat Genet* 1999; 22: 291-4.
38. GIBSON KM, HOFFMANN G, SCHWALL A *et al.*: 3-Hydroxy-3-methylglutaryl coenzyme A reductase activity in cultured fibroblasts from patients with mevalonate kinase deficiency: differential response to lipid supplied by fetal bovine serum in tissue culture medium. *J Lipid Res* 1990; 31:515-21.
39. HOUTEN SM, FRENKEL J, KUIS W, WANDERS RJ, POLL-THE BT, WATERHAM HR: Molecular basis of classical mevalonic aciduria and the hyperimmunoglobulinaemia D and periodic fever syndrome: High frequency of 3 mutations in the mevalonate kinase gene. *J Inherit Metab Dis* (in press).
40. HINSON DD, ROSS RM, KRISANS S *et al.*: Identification of a mutation cluster in mevalonate kinase deficiency, including a new mutation in a patient of Mennonite ancestry. *Am J Hum Genet* 1999; 65:327-35.
41. SCHAFER BL, BISHOP RW, KRATUNIS VJ *et al.*: Molecular cloning of human mevalonate kinase and identification of a missense mutation in the genetic disease mevalonic aciduria. *J Biol Chem* 1992; 267: 13229-38.
42. GIBSON KM, HOFFMANN GF, TANAKA RD, BISHOP RW, CHAMBLISS KL: Mevalonate kinase map position 12q24. *Chromosome Res* 1997; 5: 150.
43. HINSON DD, CHAMBLISS KL, HOFFMANN GF, KRISANS S, KELLER RK, GIBSON KM: Identification of an active site alanine in mevalonate kinase through characterization of a novel mutation in mevalonate kinase deficiency. *J Biol Chem* 1997; 272: 26756-60.
44. ÖZEN S: New interest in an old disease: Familial Mediterranean fever. *Clin Exp Rheumatol* 1999; 17: 745-9.
45. The International FMF Consortium: Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997; 90: 797-807.
46. The French FMF Consortium: A candidate gene for familial Mediterranean fever. *Nat Genet* 1997; 17:25-31.
47. CAZENEUVE C, SARKISIAN T, PECHEUX C *et al.*: MEFV-Gene analysis in armenian patients with Familial Mediterranean fever: Diagnostic value and unfavorable renal prognosis of the M694V homozygous genotype-genetic and therapeutic implications. *Am J Hum Genet* 1999; 65: 88-97.
48. BOOTH DR, GILLMORE JD, BOOTH SE, PEPYS MB, HAWKINS PN: Pyrin/marenostrin mutations in familial Mediterranean fever. *QJM* 1998; 91: 603-6.
49. MCDERMOTT EM, SMILLIE DM, POWELL RJ: Clinical spectrum of familial Hibernian fever: a 14-year follow-up study of the index case and extended family. *Mayo Clin Proc* 1997; 72:806-17.
50. MCDERMOTT MF, AKSENTIJEVICH I, GALON J *et al.*: Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999; 97: 133-44.
51. THOMAS KT, FEDER HM JR, LAWTON AR, EDWARDS KM: Periodic fever syndrome in children. *J Pediatr* 1999; 135: 15-21.
52. DE HULLU JA, DRENTH JP, STRUYK AP, VAN DER MEER JW: Hyper-IgD syndrome and pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1996; 68: 223-5.