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ORIGINAL PAPER

B cell cytopenia in two brothers with hyper-IgD and periodic fever syndrome

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Abstract We report on two brothers with hyperimmunoglobulinemia D (patient 1: serum immunoglobulin D [IgD] concentration initially 61 IU/ml, later on 340 IU/ml; patient 2: serum IgD concentration 144 IU/ml; normal <100 IU/ml, 97th centile) and periodic fever syndrome (HIDS). Both are compound heterozygous for the mevalonate kinase (MVK) mutations V377I and I268T. They developed significant B cell cytopenia (7%, 129/μl and 11%, 132/μl, respectively; normal ranges 12–22%, 300–500/μl) with hypogammaglobulinemia (IgG 5.48 g/l and IgG 5.22 g/l, respectively; normal range IgG 6–13 g/l). Furthermore, the clinical spectrum shows an interesting atypical autoinflammatory symptomatology. The therapy consisted of prednisone, azathioprine, and intravenous immunoglobulins (IVIG), which results in reduced incidence and severity of febrile attacks. Conclusion: The pathogenesis and clinical presentation of HIDS is still not fully understood and show a great variability. To our knowledge, severe B cell cytopenia in children with HIDS has not been reported before. Furthermore, the therapy of febrile episodes is still performed on an individual basis in affected patients.

Keywords Hyper-IgD syndrome · Children · B cell cytopenia · Treatment · Complications

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Introduction

Periodic fever syndromes are classified as a recurrence of febrile episodes that last from days to weeks separated by symptom-free intervals, such as familial Mediterranean fever (FMF, OMIM #249100), tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS, OMIM #142680), and hyperimmunoglobulinemia D and periodic fever syndrome (HIDS, OMIM #260920), as well as others [28]. Most of the periodic fever syndromes are hereditary diseases.

In 1984, HIDS was first described as a new entity by van der Meer et al. [31]. They reported six patients with recurrent febrile episodes of unknown origin; in all of them, increased plasma levels of immunoglobulin D (IgD) were found.

Currently, there are, worldwide, more than 180 patients identified, most of them from the Netherlands and France, but also from other countries [17, 24].

HIDS is characterized by recurrent febrile attacks that usually begin at a very early age and persist for life, although the frequency of attacks is highest in childhood and adolescence. Attacks generally reoccur every 4 to 6 weeks, with symptom-free intervals in between, though the intervals show great individual variability [9, 15]. High spiking fever continues for 3 to 7 days and is mostly accompanied by chills, cervical lymphadenopathy, and abdominal pain with vomiting, diarrhea, or both. Further symptoms include headache, hepatosplenomegaly, arthralgia, and arthritis, generally of the large joints, although arthritis in HIDS does not lead to joint destruction in contrast to juvenile chronic arthritis (JCA) [8, 11]. The most common manifestation on the skin is an erythematous maculopapulous rash [10]. There is a great individual and interfamilial variability of clinical features in patients with HIDS.

In many chronic inflammatory disorders, including hereditary periodic fever syndromes such as FMF and TRAPS, amyloidosis is a severe complication, but in HIDS, amyloidosis is very rare, despite intensive recurring inflammation [29, 30].

Typical laboratory findings are continuously elevated IgD concentrations in plasma (>100 IU/ml, 97th centile), though in some patients, serum IgD can be normal [1, 18, 26]. So far, the exact pathomechanism of IgD in HIDS remains unclear. There is a rise of acute-phase proteins, such as C-reactive protein, during febrile attacks [12]. The associated leukocytosis makes it often difficult to distinguish HIDS from an acute infection. To our knowledge, an isolated B cell cytopenia in HIDS has not been described so far.

In 1999, Houten et al. [20] and Drenth et al. [13] found that HIDS is caused by mutations in the *MVK* gene, which encodes the enzyme mevalonate kinase (MVK). The *MVK* gene is located at chromosome 12q24 [13] and is related to autosomal recessive inheritance. Cuisset et al. described a frequent occurrence of compound heterozygosity [4]. The most common mutation is V377I, which is often associated with I268T. MVK is a key enzyme in the metabolic pathway of cholesterol following directly the HMG-CoA reductase. In patients with HIDS, the MVK activity is reduced to 5 to 15% of normal, leading to increased mevalonic acid levels in the urine during attacks [4, 13, 20]. The pathogenesis of HIDS is not yet fully understood, but is presumed to find its origin in the isoprenoid pathway. Recently published findings suggest that affected patients may have overactive caspase-1, causing enhanced IL-1β secretion by peripheral blood mononuclear cells and subsequent inflammatory reactions [22, 23]. The standard treatment of HIDS remains unclear; at present, therapy is mostly supportive.

Case report

We report two Caucasian brothers with hyper-IgD and periodic fever syndrome. The parents of the children were not consanguine.

Patient 1

The first patient was diagnosed at the age of 6 years. Beginning at 15 months of age, he suffered from recurrent febrile episodes of unknown origin every second to third week with durations of 2 to 3 days and temperatures up to 40°C. During these attacks, he felt severely ill with typical symptoms of HIDS. He suffered from headaches and chills, cervical lymphadenopathy, as well as, sometimes, stomatitis and pharyngitis. A marmorated tongue was also observed. Intermittently, he complained about intense abdominal pain followed by arthralgia. The patient never presented a rash. The attacks were always accompanied by a significant rise of C-reactive protein (>300 mg/l) and leukocytosis (>20,000/nl) with 90% neutrophils. His parents reported approximately 22 febrile episodes per year over the last three years before treatment. There were often suspected bacterial infections of the upper respiratory tract that were treated with antibiotics, including a severe pneumonia. Remarkably, no specific germs could be identified.

First investigations showed normal immunologic parameters. We observed a total lymphocyte count of 24.6%, 2,830/µl (normal ranges 20–50%, 1,500–8,000/µl), T cell count was 70%, 2,313/µl (normal ranges 58–67%, 1,700–3,600/µl). His B cell count was quite normal (18%, 595/µl; normal ranges 19–31%, 500–1,500/µl), serum IgG (7.81 g/l), IgG-subclasses (IgG I 5.35 g/l, IgG II 1.97 g/l, IgG III 0.81 g/l, IgG IV 0.16 g/l), IgA (2.18 g/l), and IgM (0.7 g/l) concentrations were regular. But insufficient response to regular vaccination (diphtheria 0.5 IU/ml and tetanus 0.3 IU/ml, respectively) was found, indicating an impaired B cell function.

Serum IgD concentration was initially 61 IU/ml (normal <100 IU/ml). Therefore, a molecular analysis for HIDS was not performed initially, except for FMF and TRAPS, which showed no mutations. He was treated for six months with cimetidine under suspicion of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, without effect. A few months later, serum IgD concentration was quantified again and was found to be remarkably elevated (340 IU/ml). Urinary mevalonic acid was normal. Mutation analysis of the *MVK* gene revealed a compound heterozygosity for V377I in exon 11 and I268T in exon 9. He was started on a medication with prednisone (1.5 mg/kg/d) and azathioprine (1 mg/kg/d). Prednisone was subsequently reduced to 1 mg/d and azathioprine was raised to 2 mg/kg/d. Occasionally during the fever spikes, he was given additional prednisone (10 mg) as a single dose. Under this medication, the intervals between the febrile episodes became longer (4 to 6 weeks) and the attacks were not as severe as before, with a faster recovery after the attacks. Serum IgD concentrations increased to 620 IU/ml, without clinical correlation. Since he was started on medication, the incidence of recurrent febrile episodes was significant lower (11 per year).

In the follow-up, the child developed an isolated B cell cytopenia and hypogammaglobulinemia. Total lymphocyte count and T cell count were still normal and there were no decrease in the platelet, leukocyte, and erythrocyte counts.

At diagnosis, B cell count was quite normal (18%, 595/µl; normal ranges 19–31%, 500–1,500/µl), as well as serum IgG (7.81 g/l; normal 5–13 g/l). One year later, B cells were reduced to 12%, 217/µl (normal ranges 24–28%, 700–1300/µl) and serum IgG was 4.99 g/l (normal 6–13 g/l). Another 3 years later, B cells were found to be further

decreased to 7%, 129/µl (normal ranges 12–22%, 300–500/µl). Because of the low serum IgG (5.48 g/l) concentrations, intravenous immunoglobulin therapy was necessary.

Moreover, there were increased serum IgA values (2.94 g/l; normal 0.6–2.3 g/l) found, but regular IgM concentrations were revealed in the follow-up.

Immunologic parameters, therapy, and the course of febrile episodes are summarized in (Fig. 1).

Patient 2

The second patient was diagnosed one year after his brother at the age of 8.5 years. He presented with recurrent febrile episodes accompanied by infections of the upper respiratory tract with massive (up to 3×3 cm in diameter) and painful cervical lymphadenopathy, headaches, and recurrent abdominal complaints, especially diarrhea. The attacks were mostly interpreted as viral or bacterial infections. Beginning at the age of 1 year, these episodes reoccurred every 3 to 6 weeks and lasted about 2 to 4 days, with temperatures as high as 40°C. They were always accompanied by high concentrations of C-reactive protein (up to 366 mg/l), leukocytes of 20,000/nl with up to 90% neutrophils, and returned to normal between attacks. A severe encephalitis with somnolence, headaches, vomiting, and other typical neurological signs was diagnosed in the following course. However, no specific germ could be isolated and no pleiocytosis was detected. In the magnetic resonance imaging (MRI) scan of the brain, suspected disseminated lesions for encephalitis were found.

When HIDS was diagnosed, his total lymphocyte count was 28.8%, 2,860/µl (normal ranges 20–50%, 1,500–8,000/µl), T cell count was 75%, 2,138/µl (normal ranges 66–76%, 1,400–2,000/µl), and B cell count 17%, 485/µl (normal ranges 12–22%, 300–500/µl). Investigations of serum immunoglobulins showed normal concentrations for IgG (9.14 g/l), IgG subclasses (IgG I 6.37 g/l, IgG II 2.81 g/l, IgG III 0.78 g/l, IgG IV 0.10 g/l), IgA (2.26 g/l), and IgM (0.69 g/l). Serum IgD was elevated (144 IU/ml; normal <100 IU/ml), but urinary mevalonic acid was found to be normal. *MVK* gene analysis showed the same compound heterozygous mutations as in his brother. He was also started on prednisone (1.5 mg/kg) and azathioprine (1 mg/kg/d). Prednisone was subsequently reduced to 0.5 mg/d and azathioprine was increased to 2 mg/kg/d. Whereas febrile episodes occurred about 18 times per year before treatment, the parents reported about nine episodes per year under medication. In general, symptoms were not as severe as before therapy and the duration of the episodes became shorter (1 to 2 days). His serum IgD concentration dropped to 45 IU/ml.

Despite the reduction of episodes and severity while under treatment, one severe attack was described. The boy

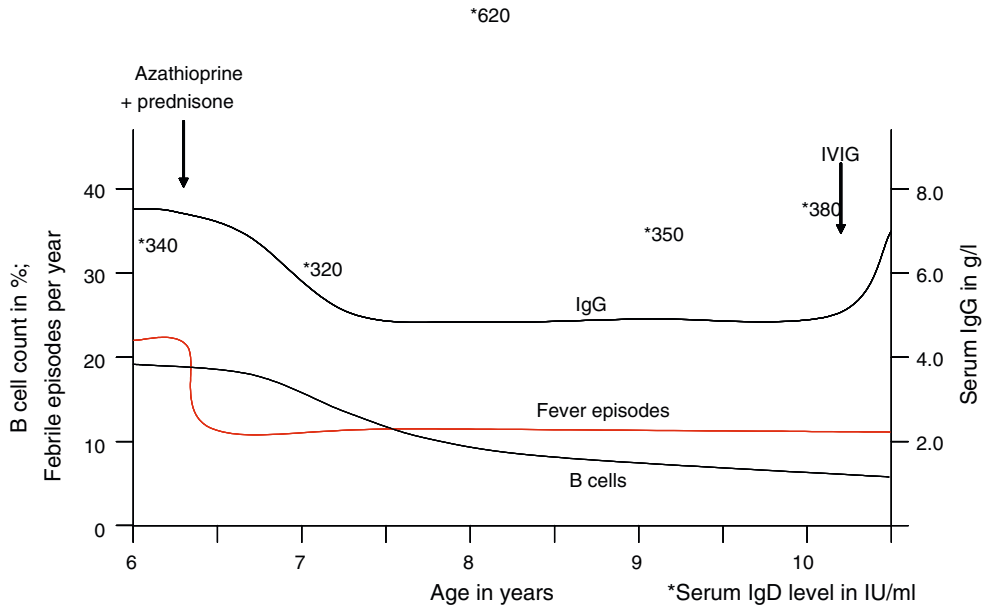

Fig. 1 In patient 1, hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) was diagnosed at the age of 6 years. He was started on a medication of azathioprine and prednisone. The number of febrile episodes decreased from 22 attacks per year before treatment to 11 episodes per year under medication. At diagnosis, B cell count was 18%. One year later, B cells were 12%. Another 3 years later, B cell count decreased to 7%. He developed a hypogammaglobulinemia. At diagnosis, serum IgG concentration was normal (7.81 g/l), but decreased in the following years to values under normal (6–13 g/l), so that starting intravenous immunoglobulin (IVIG) substitution was necessary. At diagnosis, serum IgD level was elevated (normal <100 IU/ml, 97th centile). In the following years, we observed maximal IgD concentrations in plasma of 620 IU/ml. The level of serum IgD and clinical symptoms did not correlate. At the age of 5 years, his serum IgD level was in the normal range (61 IU/ml)

acquired a mycoplasma pneumonia accompanied by clinical symptoms of severe encephalitis again. An abrupt onset of high fever with seizure, somnolence, and neurological symptoms occurred. His C-reactive protein concentration increased to 366 mg/l, but no bacteria or virus could be isolated in the spinal fluid. Antibiotics and dexamethasone were given and he recovered within one day. Serum IgG showed low values following this episode (IgG 5.22 g/l; normal IgG 6–13 g/l).

Like his brother, the patient developed isolated B cell cytopenia and hypogammaglobulinemia, but, in contrast, this patient was diagnosed to have serum IgG concentrations in the lower normal range (5.1 g/l) several months prior to the diagnosis of HIDS. Furthermore, the patient showed insufficient response to regular vaccination (diphtheria 0.3 IU/ml and tetanus 0.2 IU/ml, respectively), indicating an impaired B cell function. At diagnosis, B cell count was normal (17%, 485/µl; normal ranges 12–22%, 300–500/µl), as well as serum IgG (9.14 g/l; normal 6–13 g/l). One year later, B cells were 12%, 124/µl and his serum IgG was still in the normal range. After 3 years of treatment, B cells decreased to 11%, 132/µl. In the following course, serum IgG decreased to subnormal values (5.22 g/l). Because of the low serum IgG concentrations in combination with clinical pneumonia and severe encephalitis, we decided to treat him additionally with IVIG.

Furthermore, IgM was low (0.3 g/l; normal 0.4–1.5 g/l) but IgA was continuously normal; his total lymphocyte count and T cell count were regular and there were no decrease in platelet, leukocyte, and erythrocyte counts in the follow-up.

Immunologic parameters, therapy, and the course of febrile episodes are summarized in (Fig. 2).

Discussion

Fever syndromes are difficult to diagnose, as most of the cases show a long and devastating history until diagnosis has been made. Clinical presentations of most periodic fever syndromes are characterized by inter-individual variability [15]. With the identification of the molecular defects of the *MVK* gene, the clinical variability becomes even wider, and there were reports regarding genetically detected patients with HIDS without a rise of serum IgD concentration, which generally reflects one of the diagnostic criteria [20, 26, 31]. One of our patients also had a normal serum IgD concentration of 61 IU/ml at the time of diagnosis of HIDS. Both patients show a typical rise of C-reactive protein during febrile attacks (>300 mg/l) [12]. Furthermore, the two brothers showed clinical differences. The boy in case 2 almost always presented with a massive

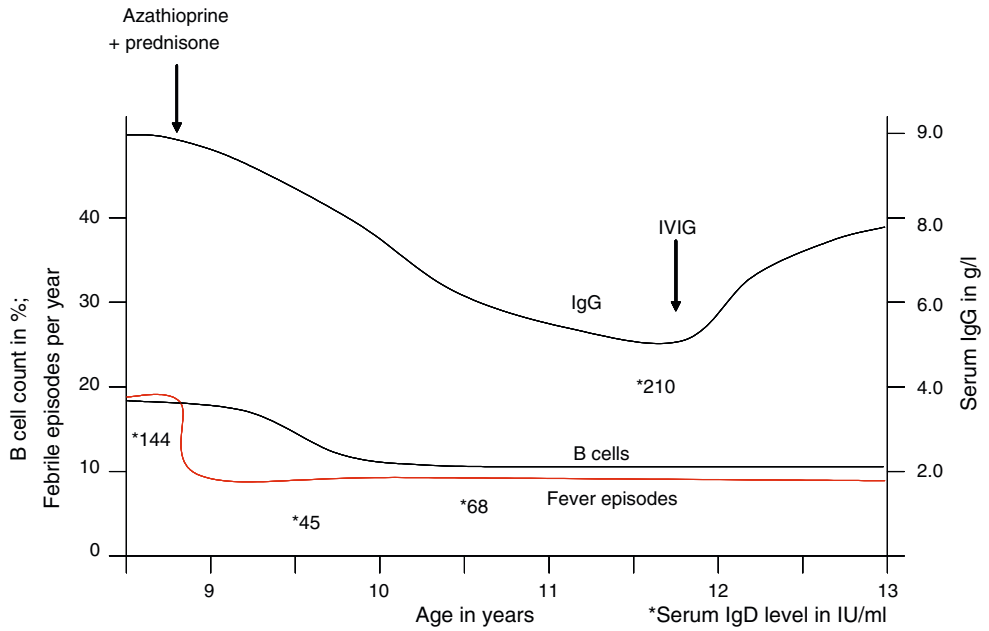

Fig. 2 In patient 2, HIDS was diagnosed at the age of 8.5 years. He was started on a medication of azathioprine and prednisone. The number of febrile episodes decreased from 18 attacks per year before treatment to nine episodes per year under medication. At diagnosis, B cell counts was 17%. In the following three years, B cell counts decreased to 11%. He developed a hypogammaglobulinemia. At diagnosis, his serum IgG concentration was normal (9.14 g/l), but decreased in the following years to values under normal (normal 6–13 g/l), so that starting intravenous immunoglobulin substitution was necessary. At diagnosis, his serum IgD level was elevated (normal <100 IU/ml, 97th centile). In the following years, we observed fluctuant, normal, and increased IgD concentrations in plasma. The level of serum IgD and his clinical symptoms did not correlate

cervical lymphadenopathy, which the boy in case 1 did not have to that extent. Chills and arthralgia could be found frequently in patient 1 but not in patient 2.

Cuisset et al. described the *MVK* mutation V377I as the most common in HIDS patients and to be often associated with I268T [4]. In patient 1 as well as in patient 2, we also detected compound heterozygosity for these mutations. Mutations in the same gene are responsible for mevalonic aciduria (OMIM #251170) and HIDS, but *MVK* mutation V377I was identified exclusively in HIDS patients [21]. Also, clinical manifestations are very different and allow a differentiation between both. Psychomotor retardation, hypotonia, dysmorphic features, failure to thrive, cataracts, and severe hepatosplenomegaly are typically found in mevalonic aciduria but are rarely found in HIDS and were not found in our two patients [17]. A deficiency of mevalonate kinase less than 1% of normal causes massively increased urine excretion of mevalonic acid, which can be seen in mevalonic aciduria [13, 19]. Whereas in patients with HIDS the activity of mevalonate kinase is reduced to 5 to 15% of normal values and, therefore, only slightly increased, mevalonic acid can be detected in urine during attacks [4, 13, 20]. Neither in patient 1 nor in patient 2 was mevalonic acid in the urine detectable, though we measured urine excretion of mevalonic acid only between febrile attacks. In addition, serum IgD concentrations are not described as increased in mevalonic aciduria, but in HIDS, it is mostly elevated.

Though mutations in the *MVK* gene that cause HIDS could be detected [13, 20], the understanding of the pathological pathway is not yet completely understood. Therefore, uniformly effective treatment does not exist and mainly supportive courses of anti-inflammatory and anti-pyretic drugs are chosen to reduce the severity of febrile episodes. Treatment trials with colchicine, corticoids, nonsteroidal anti-inflammatory drugs, IVIG, or cyclosporine have been undertaken and have shown benefit in some cases, but failed in others [9, 11, 31]. A trial in six adult patients with HIDS also showed no significant efficacy to thalidomide as an anti-inflammatory drug in the treatment of febrile attacks [14]. Simon et al. reported a positive clinical effect in 5 out of 6 adult patients with HIDS treated with 80 mg simvastatin (HMG-CoA-reductase inhibitor) for 24 weeks. In this study, simvastatin decreased the number of febrile days, but without reaching statistical significance [27].

The knowledge of the activation of the cytokine network leading to HIDS [12] may result in therapeutic trials [25]. Demirkaya et al. treated a child with anti-tumor necrosis factor with a satisfying response [7]. Anti-inflammatory treatment with the IL-1ra analog anakinra was reported to be successful in aborting the inflammatory attacks in HIDS [2] and a reduction of febrile attacks in a severe case with HIDS was described [3].

In 2001, de Dios García-Díaz and Alvarez-Blanco reported a 25-year-old woman with clinical and serological evidence for HIDS. She was treated with prednisone, which was highly and rapidly effective in aborting the attacks. Fever disappeared quickly and a dramatic clinical improvement of the remaining symptoms occurred [6].

Our patients also benefitted from treatment with prednisone. Our first-line therapy consisted of prednisone and azathioprine. By combining the two immunomodulatory medications, we hoped to reduce side effects by giving low doses. In patient 1, the number of febrile episodes decreased from 22 per year before treatment to 11 episodes per year. Moreover, an alleviation of the clinical symptoms during attacks occurred. In the case of the second boy, we also observed the effectiveness of the therapy with respect to the number of febrile attacks (18 attacks per year before treatment, about 9 episodes per year while on treatment) and the severity of symptoms. In both patients, the parents reported a faster recovery from attacks. Because the symptoms had improved clinically, we continued the first-line therapy, but since the febrile episodes did not stop completely, we are discussing the application of other substances, such as anakinra. However, anakinra is currently preferentially used in very severe cases of HIDS, despite very hopeful first reports on its use in this disease.

To our surprise, we observed in both children a significant decrease in B cell counts during follow-up, and, in parallel, a reduction of serum IgG concentrations. The reason for this B cell defect is unknown so far.

We previously reported, though in a different context, an isolated B cell cytopenia and hypogammaglobulinemia under medication with mycophenolate mofetil [16]. Theoretically, azathioprine may lead to reduced B and T cell counts, erythrocyte, leukocytes, and platelet counts [5].

Given the fact that, in our patients, no bone marrow suppression was found but an isolated B cell cytopenia, it seems to be very unlikely that azathioprine treatment is responsible for the observed phenomenon. Moreover, due to the fact that both brothers showed a B cell defect, we favor the assumption that it is more likely based on the genetic mutation of HIDS. Furthermore, in patient 2, we observed a hypogammaglobulinemia before the diagnosis and treatment of HIDS. In both patients, we observed an insufficient response on regular vaccination, indicating impaired B cell function.

The hypogammaglobulinemia in the second patient could have facilitated the occurrence of the mycoplasma pneumonia, triggering the accompanying febrile episode with high serum inflammation markers and the clinical appearance for severe encephalitis. We decided to treat the hypogammaglobulinemia with IVIG in both children.

Patients with HIDS have recurrent febrile episodes throughout their lives, though the frequency and severity

declines in adolescence [11]. The treatment of febrile episodes in children with HIDS is still unsatisfactory and is performed in most patients individually. Further studies are needed to assess the role of B cells in HIDS and the best treatment options in affected patients.

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Conflict of interest All authors declare that they have no conflict of interest.

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