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CASE BASED REVIEW

Different clinical presentation of the hyperimmunoglobulin D syndrome (HIDS) (four cases from Turkey)

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Abstract Hyperimmunoglobulin D syndrome (HIDS) is one of the autoinflammatory syndromes which are characterized by febrile attacks. Duration and frequency of the febrile attacks, as well as typical organ involvements vary greatly. Recently, it is possible to reach more reliable data by the possibilities that are opened up by molecular genetics in order to highlight the aetiopathogenesis of this group of diseases. Typical patients with HIDS have an onset of disease in the first year of life. Here, we report four Turkish HIDS cases; three of whom, the symptoms started at a later age. The diagnoses were made by relevant clinical symptoms along with MVK mutations detected by DNA sequencing method. As summarised in this article, HIDS could be presented with a broad spectrum of symptoms. Although most of the HIDS patients are reported from Europe and especially Dutch ancestry, case reports are presented from all over the world. For this reason, HIDS should be kept in mind for the differential diagnosis of periodic fever syndromes or before accepting an FMF patient as colchichine resistant. We suppose that the phenomenon of "later-onset HIDS" should shed light into unresolved clinical problems of patients with periodic fever. Especially in countries that FMF is more frequent such as Turkey, even though the symptoms start later than classic cases, HIDS should be kept in mind for differential diagnosis of periodic fever syndromes.

Keywords Autoinflammatory syndromes · Hyperimmunoglobulin D syndrome · IgD · Periodic fever syndromes

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Introduction

Hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) is a rare autosomal recessive disease, which belongs to the group of auto-inflammatory syndromes, characterized by febrile attacks. This disease was originally described in patients of Dutch ancestry by van der Meer et al. [1]. More than 90% of all cases of HIDS have been reported from the Netherlands [2, 3]. It is caused by mutations in the gene encoding mevalonate kinase (MVK), an enzyme involved in the isoprenoid and cholesterol biosynthesis pathway. The gene is located on the long arm of chromosome 12 (12q24) [4]. The four most prevalent mutations (V377I, I268T, H20P/N, P167L) accounted for 71.5% of mutations found [5].

Typical patients with HIDS have an onset of disease in the first year of life with febrile attacks of 3 to 7 days duration. The attacks generally recur every 4 to 6 weeks, but the interval between them can vary substantially in an individual patient and from one patient to another. However, beyond this typical presentation, there is a considerable variability in onset of disease and in clinical manifestations [6]. The most frequent symptoms that accompany attacks of fever are lymphadenopathy, abdominal pain, arthralgia, diarrhea, vomiting, skin lesions, and aphthous ulcers [5].

All patients elicit an acute-phase response during attacks, with leukocytosis, raised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum amyloid A. A polyclonal rise in serum IgD levels to greater than 100 KU/L is considered as the hallmark of HIDS. This is often associated with an increased serum IgA level [7]. Attacks can be precipitated by vaccination, minor infections, emotional stres, trauma and surgery, but in many instances there is no obvious trigger [8].

The differential diagnosis for HIDS is broad and includes FMF, TRAPS, PFAPA, adult-onset Still's disease, juvenile idiopathic arthritis, rheumatic fever and Behçet's disease [5].

When confronted with a patient with unexplained recurrent fever in whom FMF and TRAPS are unlikely or have been ruled out, it is advisable to test the serum IgD in conjunction with either MVK mutational analysis or biochemical assays. There is currently no agreement on a term for patients with MVK mutations but normal IgD levels, although some have advocated the term Dutch type periodic fever for patients with periodic fever and reduced MVK activity, irrespective of the IgD [9].

Here, we report four Turkish HIDS cases; all have MVK mutations homozygous or compound heterozygous detected with DNA sequencing analysis.

Case 1

We report a 34-year-old married woman with one child. Since 18 years of age, she revealed attacks of conjunctival hyperemia. For 1.5 years the patient had febrile attacks (above 38°C) accompanied by cold chills, abdominal pain, nausea and vomitting. Also, she had pharyngalgia, shortness of breath, difficulty of swallowing. Erythematous macular lesions were detected on face and arms. The attacks periodically come approximately once a forth week and lasts for 3–4 days. One year ago, she was clinically regarded as FMF and started with oral colchicine 1–1.5 mg/day but had little benefit. There is no additional diagnostic feature in her personal or family history. Her parents were non-consanguineous. Her detailed physical examination revealed erythematous lesions on the face and arm, also conjunctival hyperemia was present. Her laboratory results were as follows: during an attack (fever, abdominal pain and skin lesions); white blood cells (WBC), 24.000/mm^3; ESR, 7 mm/h; CRP, 54.43 mg/L; fibrinogen, 4.13 mg/dL; ferritin, 185 ng/mL; albumin, 3.6 g/dL. After attack, WBC, 6,600/mm^3; ESR, 6 mm/h; CRP, 12 mg/L; HBsAg, negative; AntiHCV, negative; *Brucella*, negative; *Salmonella*, negative. Her thyroid test results were normal; ANA, negative; RF, <20 IU. The PAP smear revealed minimal inflammation. The gram stain of the sputum was non-diagnostic. There was no bacterial growth on the culture of the sputum; also, it was negative for BACTEC. No bacterial growth was detected on urine culture. Several radiodiagnostic tests were performed to highlight the fever aetiology. Minimal mitral insufficiency was found on the echocardiogram. Abdominopelvic USG revealed minimal collection in Douglas pouche, splenomegaly (14 cm) and minimal pelvic dilatation on right renal collector system. Cervical USG result was normal. Thorax CT revealed thin pleural thickening on the right apical region. The PET-CT was normal. IgD is equal to 17 mg/L (radial immunodiffusion (RID), N, 5–50); IgA, 187 mg/dL (N). MEFV mutation (DNA sequencing for exon 2 and exon 10): E148Q, heterozygous; MVK mutation (DNA sequencing for exon 2, 3, 4, 5, 6, 7, 9, 10, 11 and intron 2, 3, 4, 5, 6, 7, 9, 10, 11), compound heterozygous (c.769-38 C>T; c.769-7 T>G). Fever, abdominal pain, additional compatible clinical features and MVK mutation led us to diagnose her as HIDS. She was treated with NSAIDs and corticosteroid infusion (40 mg prednisolone) during attacks and responded well.

Case 2

We present a 32 year-old married woman with two children. For 2 years the patient has complained of fever (38°C) and erythematous macular skin lesions. Headache, cold chills, nausea and malaise were the accompanying symptoms. These complaints occurred one to two times per month and lasted for 3 to 5 days. She has a history of Meniere disease, thyroiditis and operation of the lumbar vertebrae because of a bony cyst during her childhood. Her parents were non-consanguineous. Her physical examination revealed diffuse enlargement of the thyroid, scoliosis on the lumbar vertebrae and a pale erythema on the left forearm.

The laboratory tests several days after the attack were as follows: WBC, 5,540/mm^3; ESR, 14 mm/saat; CRP, 0.38 mg/dL. Unfortunately, test results during an attack were not available. Total IgE was 107 IU/mL. The TSH result was normal. The Prick tests were non-diagnostic. The C_3, C_4, C_{1Q}, C_1 esterase inhibitor were normal. ANA was negative; RF, <20 IU/mL; IgD, 15.7 mg/L (RID, N, 5–50). MEFV mutation (DNA sequencing for exon 2 and exon 10), None; MVK mutation (DNA sequencing for exon 2, 3, 4, 5, 6, 7, 9, 10, 11 and intron 2, 3, 4, 5, 6, 7, 9, 10, 11), c.769-38 C>T, homozygous. Recurrent fever, headache and skin lesion attacks along with the MVK mutation provides us to make the diagnose. She was treated with 40 mg prednisolone infusion during attacks and responded well.

Case 3

We present a case of a 23-year-old woman, single, with no child; she was complaining of fever (38°C) and abdominal pain for 6 years. Her complaints were occurring as attacks coming every 4–5 months and lasting for 4–5 days. Cold chills, nausea and vomitting, malaisea and arthralgia of the knees and ankles were accompanying the attacks. She also had frequent headaches, which deteriorated during the attacks. Her parents were non-consanguineous. Her physical examination result was normal. The laboratory findings were: during an attack the patient's WBC was 9,600/mm^3; ESR, 32 mm/h; CRP, 0.91 mg/dL. After an attack her WBC was 6,920/mm^3; ESR, 24 mm/h; CRP, 0.56 mg/dL; ANA,

negative; RF, <20 IU/mL; HBsAg, negative; Anti-HCV, negative; fibrinogen, 6.12 mg/dL; abdominopelvic USG, normal; lung radiography, normal; IgD, 30.7 mg/L (RID, *N*, 5–50); MEFV mutation (DNA sequencing for exon 2 and exon 10), none; MVK mutation (DNA sequencing for exon 2, 3, 4, 5, 6, 7, 9, 10, 11 and intron 2, 3, 4, 5, 6, 7, 9, 10, 11), c.769-38 C>T, homozygous. She was diagnosed as HIDS and treated with 40 mg prednisolone infusion during the attacks and responded well.

Case 4

We present a 9-year-old boy, born 750 g on the 28th week because of the early membrane rupture and was hospitalized for 1 1/2 months. The CRP was always found above normal levels since his birth. He was operated for strabismus on the left eye when he was 16 months old. When he was 30 months old, attacks of fever (38–40°C) started. The attacks lasted for 4 to 5 days occurring every 3–4 weeks. Mostly, pharingotonsillitis was the diagnosis. Cold chills, cervical lymphadenopathy, headache, abdominal pain, arthralgia of the knees, vomitting, diarrhea and erythematous skin lesions were the accompanying symptoms of the attacks. Antibiotherapy revealed no benefit. As he grew up, the frequency of the attacks was reduced to every 4–6 weeks.

The laboratory tests were as follows: during an attack the patient's WBC was 11,000/mm^3; ESR, 27 mm/h; CRP, 9.81 mg/dL. After an attack the patient's WBC was 8,860/mm^3; ESR, 2 mm/h; CRP, 0.801 mg/dL. No bacterial growth was found on the pharyngeal culture. The abdominopelvic USG and lung radiography were normal; IgD, 72.5 mg/L (RID, *N*, 5–50)—high—IgA, 107 mg/dL; MEFV mutation (DNA sequencing for exon 2 and exon 10), none; MVK mutation (DNA sequencing for exon 2, 3, 4, 5, 6, 7, 9, 10, 11 and intron 2, 3, 4, 5, 6, 7, 9, 10, 11), c.769-38 C>T, homozygous. Attacks of fever, characteristic of HIDS symptoms, along with MVK mutation provide the diagnosis. He is treated by NSAIDs during his attacks. Corticosteroid infusion during the attacks is recommended, but his family did not accept any other therapy.

Discussion

The periodic fever syndromes are a heterogeneous group of genetically determined diseases. They all share the common feature of cytokine-mediated autoinflammation associated with a self-limiting febrile attack. Duration and frequency of the febrile attacks, as well as typical organ involvements, vary greatly. Advances in molecular genetics permit more reliable data for the respective disease entities. Apart from the elucidation of clinical "overlap syndromes," evaluation of the different phenotypes and clinical courses also has become possible [10].

A comprehensive overview of a large cohort of HIDS patients began in 1994; it was recently published by the International HIDS Study Group. In the International HIDS Database (www.hids.net), the data were collected from patients with suspected and confirmed HIDS**.** A total of 126 patients with mutation-positive HIDS, defined as recurrent attacks of fever and at least one mutation detected in the *MVK* gene. The patients originated from 18 different countries in three different continents, although the majority of patients were European or from European ancestry (The Netherlands=47, USA=20, France=7, UK=7, Armenia, Austria, Finland, Germany, Palestine, Portugal, Turkey, Belgium, India, Kuwait, Czech Republic, Italy, Spain). The median current age of the patients was 19.0 years (mean, 24.5 years) with a range of 2–74 years. The median age of onset of symptoms was 6 months, ranging from the first week of life to 10 years. Most patients had their first attack within the first year of life (78.1%); six patients had the first symptoms after the age of 4 years [5].

There have been several case reports from the Mediterranean region and other countries. To our knowledge, five cases from Turkey were reported before. In 1991, Topaloğlu and Saatçi have reported two cases from Turkey. The first case was a 10-year-old girl who had fever attacks since 5 years of age. The IgD was high, and she was diagnosed as HIDS. She was put on colchicine with little benefit. The second case was a 9-year-old girl with recurrent fever and abdominal pain attacks since age 5. Her IgD level was elevated. A diagnosis of hyperimmunoglobulinemia D and periodic fever syndrome was made and colchicine was tried without much improvement [11].

In 2004, Çoban and Terzioğlu have reported a patient with HIDS. She was a 17-year-old Turkish girl with complaints of fever, abdominal pain, arthralgia and headache. Her first symptoms started in early childhood. Earlier she was diagnosed as FMF with no response to colchicine treatment. Her acute phase reply and IgD was above normal. She had a heterozygous M680I mutation. Genetic analysis for MVK mutation could not be performed. She was diagnosed with HIDS clinical symptoms, laboratory results and poor response to colchicine therapy [12].

In 2007, Demirkaya et al. have reported a patient with HIDS. A 6-year-old girl had febrile attacks, abdominal pain, maculopapular rash and diarrhea that started in infancy. The plasma immunoglobulin levels (IgG, IgM, IgA and IgD) were elevated. The mutation analysis of mevalonate kinase revealed homozygous c.829 C>T (R277C). Based on this, a diagnosis of HIDS was proposed. She has had a very severe disease manifestation with growth failure, hepatosplenomegaly,

very frequent attacks but was not mentally retarded. She was demonstrated as the most severe Turkish HIDS case reported so far [13].

In 2008, Topaloğlu et al. have reported a 20-month-old referred to the hospital for evaluating the aetiology of hepatosplenomegaly and abdominal pain. Due to recurrence of attacks and common frequency of FMF in Turkey, MEFV mutation was obtained, was found to be only heterozygous for E148Q with no response to colchicine, and his attacks resembled HIDS with high IgD level and high urine mevalonic acid levels during the attack. He had been on etanercept therapy with great improvement of attacks but the hepatosplenomegaly was persistant [14].

Hammoudeh reported the first HIDS case from Arab countries in 2005, a 9-year-old Palestinian boy with recurrent attacks of fever since 8 months of age. The DNA sequence analysis showed homozygous V377I mutation for *MVK* gene confirming the diagnosis of HIDS [15].

D'Osualdo et al. have studied 136 individuals affected with recurrent fever of unknown origin. Following analysis of the *MVK* gene, 15 patients (nine males and six females) were demonstrated to carry mutations in either homozygous or compound heterozygous state. In all, 13 patients were of Italian origin, in addition to one Polish and one Albanian. The febrile attacks appeared within 1–24 months of age and 11/15 patients developed the disease before ageing 1 year [16].

Abreu et al. have reported the first Portuguese case report of HIDS, a 25-year-old woman with periodic fever since she was 8 months old. She had high serum IgD levels and was compound heterozygous: V377I and T237S for MVK and diagnosed as HIDS [17].

In 2009, Naruto et al. have discussed the case of a 15-year-old Japanese girl who had presented with periodic fever, hepatosplenomegaly and intractable diarrhea from 7 weeks of age. The patient had extremely elevated levels of mevalonic aciduria and had homozygosity as a novel mutation in the *MVK* gene (G326R). Finally, HIDS was diagnosed. She was treated with simvastatin, which resulted in a moderate decrease of the urinary mevalonic acid concentration and good clinical course. This is the first case in which homozygosity for the mutation of the *MVK* gene has been reported in an Asian patient [18].

As several of them summarized above, to our knowledge, all cases in the literature were reported with the onset of the disease in the childhood. However, three out of four of our cases started at a later age. These results bring into our minds that a subtype of HIDS could be present.

Table 1 Clinical features of the cases

	Case 1	Case 2	Case 3	Case 4
Current age (years)	34	32	23	10
Sex	F	F	F	M
Age of onset (years)	18	30	17	2.5
Frequency of attacks (weeks)	4	3–4	4–5	3–4
Mean duration of attacks (day)	3–4	3–5	4–5	3
Starting factors	Stress	–	Stress	Vaccination, minor infection, stress
Fever	+	+	+	+
Lymphadenopathy	–	–	+	+
Abdominal pain	+	–	+	+
Arthralgia	–	–	–	+
Diarrhea	–	–	–	+
Vomitting	+	–	+	+
Skin lesions	+	+	–	+
Headache	–	+	+	+
Cold chills	+	+	+	+
Arthritis	–	–	–	–
Aphtous ulcers	–	–	–	+
Pharingitis	+	–	–	+
Splenomegaly	+	–	–	–
Hepatomegaly	–	–	–	–
Serositis	+	–	–	–
MEVF mutation	+	–	–	–
MVK mutation	+	+	+	+

Case 1 has a MEVF mutation (heterozygous E148Q). Partial response to colchicin has led us to approve the diagnosis. Additional clinical and laboratory investigations provided data for HIDS diagnosis. Therefore, HIDS should be considered for the differential diagnosis of adult patients for colchicine-resistant FMF and also the other periodic fever syndromes even though the symptoms are milder and/or the age of onset is later than usually expected.

As exclaimed before, HIDS is a disease that may reveal different phenotypic features as one form is called as Dutch type periodic fever. Environmental and racial factors may have affected the phenotypic presentation of the disease as age of onset and immunoglobulin levels. Our paper suggests that, although the greater portion of diagnosis is put in European countries especially to Dutch patients, HIDS should be considered for the differential diagnose of periodic fevers in the other countries.

In case 4, a 9-year-old boy revealed typical HIDS symptoms accompanying high IgD, whereas the remainder cases whom all adult patients revealed milder symtoms and normal IgD. Previously, it was shown that the disease tends to improve with age, as attacks become less frequent (5, 8). Unfortunately, it is not clear how the IgD levels change with age. It could be hypothesized that as the symptoms get milder, IgD levels could be reduced correlately. But this hypothesis needs to be proven by cohorts of the HIDS patients. Also, as mentioned before, this is not obligatory for the diagnosis. The clinical findings that usually associate with HIDS actually correlate better with the presence of MVK mutations than with high IgD levels [4].

All of our cases have c.769-38 C>T (Three cases homozygous and one is compoud heterozygous). This mutation is defined as symptomatic for disease-related symptoms by Touitou et al. (see Infevers Database at http://fmf.ign.cnrs.fr/infevers) and commented as sequence variant frequent in the general population.

The limitation of our report is urine mevalonic acid and serum mevalonate kinase levels could not be tested. But positive diagnostic genetic testing with the relevant clinical features obtain the diagnosis of HIDS.

We suppose that the phenomenon of later-onset HIDS should shed light into unresolved clinical problems of patients with periodic fever. Especially in countries that FMF is more frequent such as Turkey. Even though the symptoms start at a later age or the serum levels immunoglobulin D and/or A are normal, HIDS should be kept in mind for differential diagnosis of FMF, for colchicine-resistant FMF and other periodic fever syndromes.

Disclosures None.

Conflict of interest The authors declare no conflict of interest.

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