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CASE REPORT

Hyper-IgD syndrome with novel mutation in a Japanese girl

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Abstract Hyperimmunoglobulin D and periodic fever syndrome (HIDS) is an autosomal recessive auto-inflammatory disorder characterized by recurrent febrile attacks with lymphadenopathy, abdominal distress, skin eruptions and joint involvement. We discuss the case of a 15-year-old Japanese girl who had presented with periodic fever, hepatosplenomegaly and intractable diarrhea from seven weeks of age. At first, undifferentiated autoimmune disorder was suspected, and she was treated with prednisolone and, in turn, with immunosuppressants such as cyclosporine, methotrexate, cyclophosphamide and rituximab or with plasma exchange. However, these trials failed to relieve her symptoms, and so she was transferred to our hospital when she was 15 years old. Her parents and elder brother had no history of recurrent fever, prolonged abdominal pain or diarrhea of unknown origin. 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, and indicated a need for differentiation.

Keywords Hyper-IgD syndrome · MVK · Periodic fever syndrome · Simvastatin

Introduction

Hyperimmunoglobulin D and periodic fever syndrome (HIDS) is an autosomal recessive auto-inflammatory disorder characterized by recurrent febrile attacks with lymphadenopathy, abdominal distress, skin eruptions and joint involvement [1–3]. Symptoms appear in early infancy and may persist throughout life with gradual increases of serum IgD levels [4, 5].

We recently encountered an HIDS patient with homozygosity as an MVK G326R mutation. The patient was treated with simvastatin, which brought about decreases in both the urinary mevalonic acid concentration and in the number of febrile days.

Case

A 15-year-old Japanese girl had presented with periodic fever, hepatosplenomegaly and intractable diarrhea from seven weeks of age. She had initially been treated with antimicrobial agents and central venous nutrition because of recurrent fever and frequent diarrhea in a regional hospital. She had body rashes at 2 years, arthritis at 5 years and headaches at 6 years. Febrile episodes, peripheral blood leukocytosis and C-reactive protein elevation (more than 10 mg/dl) were observed almost every other week. Then, an undifferentiated autoimmune disorder or systemic-onset juvenile idiopathic arthritis (JIA) was suspected, and she was treated with daily prednisolone at two years old. However, the corticosteroid administration

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did not improve the febrile episodes, so she was treated in turn with plasma exchange and immunosuppressants such as cyclosporine, methotrexate, cyclophosphamide and rituximab. However, these attempts failed to suspend her recurrent fever, abdominal pain and diarrhea.

Then, she was transferred to our hospital at the age of 15. The adverse events due to long-term, high-dose corticosteroids were marked, and physical examination revealed short stature and obesity (height 98.2 cm, −11.5 SD; weight 29 kg, −3.0 SD), secondary diabetes mellitus (hemoglobin A1c 7.6%), osteoporosis (BMD −4.88SD), multiple compression fractures of the spine, and glaucoma. Neither her parents nor her elder brother had any history of recurrent fever, prolonged abdominal pain or diarrhea of unknown origin. Her laboratory results at admission showed high leukocyte counts (15,000–20,000/ μl), C-reactive protein levels of 3.0–10.0 mg/dl, a serum IgG level of 1,124 mg/dl, serum ferritin 483 ng/ml, and high levels of serum IgD (38.6 mg/dl; normal range <9.0 mg/dl), and extremely high mevalonic aciduria (27,422 μg/day; normal range 92.8–674.5 μg/day) (Table 1). Antinuclear antibody, rheumatoid factor, anti-mitochondrial antibody and anti-LKM-1 antibody were all negative. The following serum cytokine levels in the febrile period: interferon gamma, <0.1 IU/ml; interleukin, (IL)-6 56.5 pg/ml; soluble IL-6R, 30.4 pg/ml; tumor necrosis factor (TNF)-alpha, 1.9 pg/ml; soluble TNFR1, 2,120 pg/ml; soluble TNFR2, 3,870 pg/ml; and IL-1 beta, <10 pg/ml. In addition, the site of inflammation was examined by 18F-FDG-PET, but there were no abnormal findings.

Finally, by the clinical findings and the genome analysis as indicated below, she was treated with simvastatin, which resulted in a moderate decrease of the urinary mevalonic acid concentration, and periodic fevers were relieved. Depending upon the gradual tapering of corticosteroids, secondary complications were subsided and especially she needed no more steroids.

Table 1 Laboratory data at admission in our hospital

WBC	15,900 μl^{-1}	IgG	1,124 mg/dl
Neu	92.5%	IgA	266 mg/dl
Lym	5%	IgM	45 mg/dl
Hb	13.1 g/dl	IgD	38.6 mg/dl
Plt	45.4 × 10^4 μl^{-1}		
ESR	64 mm/h	*Cytokine profile*	
AST	49 IU/l	IFN-γ	<0.1 IU/ml
ALT	95 IU/l	IL-1β	<10 pg/ml
LDH	471 IU/l	IL-6	7.0 pg/ml
Glu	125 mg/dl	sIL-6R	29.5 pg/ml
HbA1c	7.6%	TNF-α	1.0 pg/ml
CRP	4.1 mg/dl	sTNFR1	1,110 pg/ml
Ferritin	483 ng/ml	sTNFR2	2,080 pg/ml

After informed consent was obtained, peripheral blood samples were collected from the patient and her parents, and genomic DNA was extracted from the mononuclear cells and screened for the MVK gene using the QIAamp blood mini kit (QIAGEN, Hilden, Germany). Total RNA was also extracted using RNeasy Mini Kit (QIAGEN). Ten encoding exons (from 2 to 11) in the MVK gene were analyzed by PCR amplification and the direct sequencing method. We found homozygosity for a mutation, GGA to AGA, in codon 326 of exon 10 of the MVK gene. This mutation (G326R) results in the replacement of glycine by arginine in the mevalonate kinase (Fig. 1). Gene analysis was also performed in the patient's mother and father, and we found one heterozygote for mutation (GGA/AGA in codon 326 of exon 9) (Fig. 1) in the MVK gene of both parents. This result finally made possible the diagnosis of hyper-IgD and periodic fever syndrome.

Discussion

Hyperimmunoglobulin D and periodic fever syndrome was diagnosed in a Japanese girl by gene analysis as well as from the clinical symptoms and signs. The patient had been suffering from an unknown chronic fever and diarrhea for almost 15 years without any appropriate diagnosis. The corticosteroids and immunosuppressants with which she had been treated failed to improve her condition—indeed, most her problems at admission in our hospital were due to adverse events secondary to long-term corticosteroid administration. Her reaction to simvastatin treatment, accompanied with tapering of the corticosteroids, which was carried out in place of the unnecessary long-term corticosteroid therapy, yielded favorable results. The gene responsible for her affliction was found in our laboratory to be a homozygous mutation, G326R, of the MVK gene.

HIDS is a rare, apparently monogenic, autosomal recessive disorder characterized by recurrent episodes of fever accompanied with lymphadenopathy, abdominal distress, joint involvement and skin lesions. In 1984, Van der Meer and colleagues first described the periodic fevers and constantly elevated polyclonal IgD in six patients and labeled the syndrome. This disease must be distinguished from other clinical entities with recurrent high-spiking fevers such as systemic-onset JIA and adult-onset Still disease [6, 7]. The fever begins in infancy and accompanies repeated episodes of inflammation every 4–6 weeks, continuing for about 1 week each time. However, there were no symptoms between the episodes of inflammation. About two-thirds of cases exhibit stomachache, diarrhea, vomiting, arthralgia or nondestructive arthritis, various exanthemata, and cervical lymphadenopathy. The causal gene was identified as an MVK gene, and the gene product,

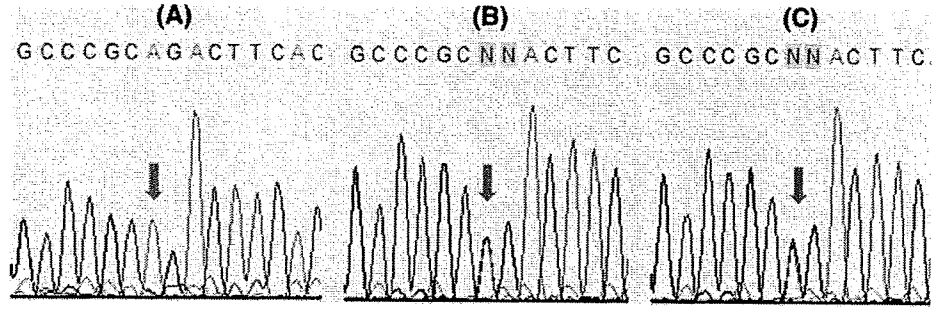

Fig. 1 MVK gene analysis in the patient (a) and in her mother (b) and father (c). In the patient, the 1012G > A transition (G326R) in codon 326 (*arrow*) converts a glycine (G) to arginine (R). The patient is homozygous for this mutation (*arrow*), and both her mother and father are heterozygous (*arrow*)

mevalonate kinase (MVK), is a metabolic enzyme produced during cholesterol synthesis [4, 5, 8]. It presents a recessive hereditary form, and the phenotype was thought to be different from that of the mevalonic aciduria, which is a congenital metabolic abnormality similar to the abnormality of the gene [9]. Although HIDS is classically defined as a high concentration of mevalonic acid in the urine, it is characterized by a high serum IgD concentration during each febrile episode, but some reports from the Netherlands stated that high levels of serum IgD were not seen and affirmed that other diseases also showed high serum IgD levels [10]. Thus, it is now common practice to examine the MVK gene in order to diagnose this disease.

A recent genome study revealed the linkage of HIDS to the gene encoding for MVK, a homodimeric enzyme present in the peroxisomes of mammalian cells, causing very elevated urinary excretion of mevalonic acid [11]. Over 80% of patients with HIDS were reported to have compound heterozygous mutation in the MVK gene. Among patients with HIDS, only one patient with heterozygosity in the form of the MVK G326R mutation was reported [12]. This unique heterozygosity, compounded with V377I, has previously been found to be associated with HIDS. This paper is the first report about the homozygous MVK mutation G326R in a Japanese patient with HIDS.

The patient's clinical manifestations and laboratory findings, such as the high levels of serum IgD and increased levels of urinary mevalonic acid, as well as the favorable effects of simvastatin all together suggested that the relationship of gene mutation and HIDS was a causal one. Her mother and father were both found to have heterozygosity as the MVK mutation G326R, but this was not compounded with any other missense mutation. According to the autosomal recessive hereditary trait, the parents are phenotypically silent, but their daughter is affected due to the MVK homozygosity mutation.

Cuisset L. et al. [13] previously reported a HIDS case with heterozygous mutation in the MVK gene, G326R, compounded with V377I. Of 25 HIDS cases, two had homozygosity for the MVK genes, P167L and I268T. The present case is a further instance of homozygous mutation in the MVK gene. V377I mutations, both compound heterozygous and homozygous mutations, generally result in a slight reduction of the stability of recombinant mevalonate kinase protein and in the catalytic activity of the enzyme, and the activity of mevalonate kinase is reduced to 5% to 15% of normal. The phenotypical differences between compound heterozygous and homozygous mutations are thought that there is no difference.

Various drugs have been tried for the treatment of HIDS, but no effective cure has yet been established [14]. It is said that colchicine, steroids, immunoglobulins, cyclosporine, and thalidomide are ineffective, and they were administered in this case, but were indeed ineffective. It should also be added that mizoribine, methotrexate, cyclophosphamide, rituximab and plasma exchanges were also ineffective in this case. In the literature, simvastatin [15] and etanercept [16] are said to be partially effective. Simvastatin, a HMG-CoA inhibitor, acted by obstructing the synthesis of mevalonic acid in the upper reaches of the metabolic pathway for cholesterol synthesis. In addition, Lazzerini et.al. suggested that this drug significantly inhibits the production of IL-6 and IL-8 also in IL-1-stimulated fibroblast-like-synoviocytes via an HMG-CoA-reductase block by means of an interference in the prenylation process and NF-κB activation [17]. Etanercept is an inhibitor of TNFα, and it was reported that it was effective in shortening the duration of the fever by suppressing the work of TNFα. In this case, it might be IL-6 that caused the inflammation. Therefore, it appears that pharmaceutical blockage of IL-6 is a therapy that should be tried in the future.

In conclusion, in Japan, cases of HIDS may so far have been overlooked or misdiagnosed as infectious diseases or autoimmune disorders, especially systemic-onset JIA. Our patient's case suggested to us the need to establish an investigation and information system to enable proper diagnosis of autoinflammatory diseases to be made in Japan and in other Asian countries.

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Conflict of interest statement We declare that we have no conflicts of interest.

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