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Clinical Report

Hyper IgD and periodic fever syndrome in Japan

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Abstract

Recently, an increasing number of autoinflammatory diseases showing periodic fever have been reported. In order to investigate the actual condition regarding the diagnosis and occurrence of Hyper IgD and periodic fever syndrome (HIDS) in Japan we sent out questionnaires about patients including suspected cases. Eight cases including 4 suspected cases were collected from 8 different institutes. Only one case had genomic mutation. Although the data coincide with those of HIDS, we concluded that typical cases of HIDS were quite rare in Japan in terms of the age of occurrence and aphthous stomatitis.

Introduction

Recently, an increasing number of autoinflammatory diseases showing periodic fever have been reported in Japan. Among them hyperimmunoglobulin-D syndrome (HIDS) is a representative genetic disorder characterized by recurrent febrile episodes typically associated with lymphadenopathy, abdominal pain, and an elevated serum polyclonal IgD level (OMIM #260920). It has mainly been described in The Netherlands and France, although the international registry includes a number of cases from other countries. At least 180 patients with HIDS have been reported worldwide. HIDS is classified into a classic type which is defined to show a mutation of the mevalonate kinase (*MVK*) and a non-classic type without mutation of *MVK*[1)]. The activity of mevalonate kinase is reduced to 5-15% in HIDS patients. Most classic types of cases are compound heterozygous for 2

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Table 1. Profile of patients

number of patients	1[10]	2	3[11]	4	5	6	7	8
definited or suspected cases judged by physician	definitive	definitive	definitive	definitive	suspect	suspect	suspect	suspect
hospital	Yokohama	Oosaka	TMU	Yamanashi	Kagoshima	Keio	Kanazawa	Fukui
age	16	8	6	13	10	10	11 months	7
gender	F	M	F	M	F	M	M	M
family history	none	unknown	allergy	none	none	mother	none	father
underlying medical condition	none	anhidrotic ectodermal dysplasia	none	none	none	none	low birth weight	none
birth weight	unknown	3,072	3,020	1,526	3,284	2,715	1,810	2,760
occurrence	1 year	1 month	2 years and 7 months	8 years	4 years and 7 months	7 years and 8 months	9 months	3 years
fever	7 days every 2-4 weeks	+	2-7 days every 4-6 weeks	3-5 days every 2-4 weeks	1-5 days every 12 weeks	1-4 days	+	+
lymphoadenopathy		+	+	+	-	+		-
abdominal symtoms	+	+	+	+	-	-		
rash	+	+	-	-	+	+	-	-
arthralgira/arthritis	+	-	+	-	+	+	-	-
tonsilitis	-	+	+	+	+	+	-	+
apthus stomatitis	-	-	+	-	+	+	-	+
others	headache					cough	monoclonal protein band	pain of musculus gastro-cnemius
ESR		>140	91	48	80	54	35	24
white blood cells (microl)	23,900	33,040	10,800	11,800	8,900		9,600	7,200
CRP (mg/dl)	14.5	37.8	15.2	17.57	10.49	7.67		16.5
IgD (febrile period, mg/dl)	47	73.1	16.9	48.8	101.7	36.6	129	27.5
IgD (unfebrile period mg/dl)	38.6		14.9	38.6	128	42.3	100	18.7
IgA (mg/dl)	303	1530	115	216	421	238	190	113
IgG (mg/dl)	1,732	1,060	1,591	1,606	2,596	1,310	638	923
SAA (mg/dl)	2,370	347	1,100			37		
sIL-2 receptor (U/ml)		770	921			615		
thrombocytemia	+	-	-	-	-	-	-	-
clotting abnormality	+	-	+	-	-	-	-	-
liver dysfunction	+	-	-	-	-	-	-	-
IL-6 (pg/ml)	15.1	38.6	15					
sTNF-R1(pg/ml)	2,060	1,420				919		698
IL-1beta (U/ml)	<10							
urinary mebalonic acid (ng/ml)	27,560	178	115			109		
antibiotics	none	effective	none	effective	none	none	none	none
corticosterioid	effective	effective	not done	not done	none	not done	not done	effective
genomic study	G326R	negative	negative	not done	not done	negative	not done	not done
prognosis		improved after 5 years		improved after 12 years			died at 11 months by malignnt hyper-ther-mia	improved after 7 months
outcome		improved after 5 years		improved after 12 years			died at 11 months by malignnt hyperthermia	improved after 7 months

different defects in the MKV gene. Various types of mutations have been identified, including missense, nonsense, frame-shift, and short interstitial deletions. One mutation, V337I, is present in more than 80 percent of patients. The V337I mutation results in a slight reduction of the stability and in the catalytic activity of the enzyme. However, the etiology of the non-classic type of HIDS is unknown. On the other hand, mevalonic aciduria (MVA) is also an autosomal recessive inherited deficiency of mevalonate kinase, in which the activity of mevalonate kinase is below 5%[2].

In Japan only one case of HIDS, confirmed by genomic study, has been reported so far. In order to investigate the actual situation of the diagnosis and occurrence of HIDS in Japan we sent out questionnaires about patients with HIDS, including suspected cases, to 25 departments of pediatrics and institutes which are familiar with immunodeficiency and immunological diseases.

Eight cases (5 boys and 3 girls) including 4 suspected cases were collected from 8 different institutes. There were 2 cases with family histories of periodic fever, a case with hypothyroidism and another case with anhidrotic ectodermal dysplasia. Two patients were premature babies weighting 1526 and 1810 gram at birth. Symptoms occurred from 1 month to 8 years (mean 40.1 months), and periodic fever appeared one to seven days every two to four weeks. Other symptoms included: lymphoadenopathy (4/6 cases), abdominal symptoms (5/6 cases), rash (4/8 cases), arthralgia or arthritis (4/8 cases), hepatosplenomegaly (3/8 cases), tonsillitis (6/8 cases), apthus (4/8 cases) and others (1 each of myalgia of the musculus gastrocnemius, productive cough, and headache).

Laboratory findings revealed elevated acute-phase reactants (erythrocyte sediment rate, white blood cell counts and the levels of CRP were 54±39.7/hr, 10,800±9658/μl and 15.2±9.76 mg/dl, respectively) during febrile periods. Serum IgD levels were 47.9±38.5 mg/dl (100 U/ml=14.1 mg/dl) in febrile periods and 38.6±45.2 mg/dl in non-febrile periods. Serum IgA levels were 245±469.6 mg/dl, IgG 1450±602.7 mg/dl, and those of serum amyloid A 723±1038 mg/ml (control <8 μg/ml). Soluble IL-2 receptor levels were 770±153.0 U/ml (control <505 U/ml), and those of soluble TNF R1 were 1169±604 pg/ml (control 749-1966 pg/ml). IL-6 levels were 15.1±13.6 pg/ml (control <6 pg/ml). The urinary excretion of mevalonic acid was high in 4 cases examined. A genomic study of MVK was done in 3 cases, and only 1 case revealed positive result (G326R). Corticosteroids were effective in 3 out of 4. One patient died and three improved by aging.

According to Drenth et al.'s report HIDS is typified by a very early age at onset (median, 0.5 years)[3], and the patients in this report were not common cases, especially cases 4 and 6. Their symptoms were similar to other diseases of periodic fever with aphtous pharyngitis adenitis (PFAPA), familial mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), Crohn disease, and Bechet disease. Symptoms of FMF, Crohn disease and Bechet disease usually appear at a later age. It is difficult to diagnose HIDS in patients with PFAPA and TRAPS from the symptoms. Unlike PFAPA, abnormal symptoms, especially vomiting (56%) and diarrhea (82%), are dominant features, and 80% have polyarthralgia[4]. Four cases in this report had aphthous stomatitis. TNFR1 which is known as a disease marker of TRAPS was assayed in 4 cases and the concentrations were below 1,000 pg/ml during the non-febrile period in two cases. Their IgD levels and mevalonic acid in urine were constantly high. Although the data coincide with those of HIDS, we concluded that typical cases of HIDS were quite rare in Japan in terms of the age of occurrence and aphthous stomatitis. Yoshimura et al. reported a boy having periodic fever since 3 years and 2 months[3], and Okamoto reported another case aged 4 years who showed periodic fever and ectodermal dysplasia[6]. None of the reports however, mentioned the concentration of mevalonate or genomic studies of mevalonate kinase. The gene variation of *MVK* which are known, are V377I/I268T/P167L/H20P/A344T as the main amino acid variation of *MVK*. V377I is the most frequent mutation with amino acid change[1)7)]. According to the study of Cuisset et al. they found 20 out of 25 unrelated cases showing V377I[7]. In our study only one case had a mutation of *MVK*. An assay of mevalonic acid kinase would help to diagnose the non-classic form of HIDS[8]. Case 1 showed extremely high mevalonic acidurea compared with other cases. Case 1 is the only patient with genomic mutation, therefore, definite cases of HIDS are quite rare in Japan and case 1 might be classified as mevalonate kinase deficiency. To conclude, the genomic studies of all exons including the promotor region should be done in all suspected cases, especially in cases with a family history. More genomic studies would help to conclude this.

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本邦における高 IgD 症候群のアンケート調査

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近年、周期性発熱をきたす自己炎症性疾患の報告が多数みられるようになってきている。本邦における高 IgD 症候群の実態を知るため、疑い例を含めてのアンケート調査を行った。異なる施設より疑い例を含めた 8 症例が集積されたが、1 例のみ遺伝子検索にて確認された症例であった。本邦においては臨床症状は高 IgD 症候群に類似する症例は存在するが、典型的な高 IgD 症候群は極めてまれであると考えられた。

〈キーワード〉 高 IgD 症候群、メバロン酸キナーゼ、血清アミロイド A、尿中メバロン酸