Familial Mediterranean Fever and Hyperimmunoglobulinemia D Syndrome: Two Diseases with Distinct Clinical, Serologic, and Genetic Features

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ABSTRACT. ***Objective.*** To determine whether the 2 periodic febrile syndromes familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D syndrome (HIDS) are distinct diseases.
Methods. Clinical manifestations of the diseases were analyzed by physicians experienced with FMF and HIDS. Serum immunoglobulin (Ig) levels were studied in 70 patients with FMF using nephelometry or ELISA and compared with Ig levels in 50 patients with HIDS. Genetic linkage of HIDS with the chromosome 16 polymorphic locus RT70, currently used for refined localization of the FMF susceptibility gene (MEFV), was studied in 9 HIDS families (18 patients) using polymerase chain reaction amplification and gel electrophoresis.
Results. The main clinical features distinguishing FMF from HIDS were lymphadenopathy, skin eruption, and symmetrical oligoarthritis in HIDS, and monoarthritis, peritonitis, and pleuritis in FMF. Increased IgG levels were found in 12 patients with FMF (17%), IgA in 16 (23%), IgM in 9 (13%), and IgD in 9 (13%), significantly lower than the prevalence reported for HIDS. We found no evidence for genetic linkage between HIDS and the chromosome 16 marker RT70.
Conclusion. HIDS and FMF are different entities, clinically, immunologically, and genetically. (*J Rheumatol 1997;***24:1558–63**)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEVER HYPERIMMUNOGLOBULINEMIA D SYNDROME
IgA IgD CHROMOSOME 16 MEFV

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of febrile serositis, mostly peritonitis, arthritis, and pleuritis[1]. Although immunologic, serologic, and metabolic factors have been studied[2–9], the pathogenesis of FMF is still not known. The recent mapping of the FMF susceptibility gene, designated MEFV, to chromosome 16p[10], permits elucidation of the molecular lesion underlying the disease by positional cloning.

Hyperimmunoglobulinemia D syndrome (HIDS) is another autosomal recessive periodic febrile syndrome, characterized by febrile attacks of abdominal and joint pain[11]. While its resemblance to FMF is striking, there are suggestions that it is a clinically, serologically, and genetically distinct entity[11–13]. However, more data to support HIDS's uniqueness are required, as studies distinguishing the 2 diseases are limited and based on a small population of patients with FMF[11]. Moreover, progressive narrowing of the FMF candidate interval permits reexamination of genetic linkage data on HIDS families. An earlier study[12] used haplotype analysis with 4 markers from MEFV region of chromosome 16p, but the closest marker on the centromeric side of MEFV was roughly 10 cM from the gene. We took advantage of a newly identified marker about 1 cM centromeric to MEFV to perform linkage studies in HIDS families. In addition, we established a collaborative study among our centers to compare the clinical and immunological features of FMF and HIDS.

MATERIALS AND METHODS

Comparative analysis of clinical manifestations. Representatives of the FMF clinic of Sheba Medical Center and the HIDS clinic at the University Hospital of Nijmegen and the HIDS study group who personally attend patients with the diseases met at Nijmegen to study the manifestations of

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the 2 diseases for similarities and differences by reviewing and discussing the clinical presentation of the diseases. The analysis was based on experience with 50 patients with HIDS treated by physicians of the hyper-IgD study group for the last 15 years, and about 4000 patients with FMF followed over the last 40 years as part of an ongoing study in the FMF clinic. Clinical features of these patients have been reported[1,11,14,15] and recently updated[13,16].

Determination and comparative analysis of immunoglobulin levels. Seventy consecutive patients with FMF, attending the FMF clinic for routine followup examination, donated 10 ml blood. All were following a continuous colchicine regimen. Before starting colchicine all had clinical manifestations agreeing with the criteria for FMF[1,17]. At the time of blood donation, they were free of attacks. No patient had, in addition to FMF, a recognized acute or chronic allergic, inflammatory, or infectious condition leading to hyperglobulinemia. After clot formation, the serum was separated and kept at –20°C until studied.

IgD level was studied by ELISA as described[18]. Briefly, microtiter plates were coated with rabbit antihuman IgD antibody, and sera and standard solutions with known concentrations of IgD as reference were added. The presence of IgD was detected by addition of monoclonal IgG antihuman IgD followed by peroxidase conjugated, antimouse IgG and substrate. The absorbency was read using an ELISA reader and the level of IgD in sera was determined with reference to the standard solutions. Levels of the IgG, IgM, and IgA were studied using nephelometry (Cobas Fara, Roche Diagnostics, Basel, Switzerland). The immunoglobulin levels in 70 FMF and 50 HIDS sera were compared. Ig levels in HIDS sera were determined previously by the same laboratory, personnel, and methodology as in the current study and were reported as part of a large clinical and laboratory study of these patients[13].

Determination of the linkage between HIDS and RT70. DNA samples were obtained from members of 9 HIDS families, consisting of 18 patients and 26 first degree relatives. Their pedigrees and genomic DNA preparation have been reported[12]. The diagnosis of HIDS was made according to published criteria[12]. These families were genotyped for a newly described tetranucleotide-repeat marker derived from cosmid RT70, which is located within 1 cM of MEFV on chromosome 16p. Five alleles of this marker were identified in the general population[19].

RT70 polymerase chain reaction (PCR) primers were synthesized as follows: 5′-TCACTCTAGCTTGGGTGAAGG-3′ and 5′-CCTCTCCAGAGGACAACTGG-3′. The PCR reactions were carried out in a volume of 10 µl. The reaction mixture consisted of the pair of primers (0.1 µl of 150 ng/µl each), [^{32}P] labeled primer [0.05 µl from a 15 µl reaction mix containing 187.5 ng 5′ primer, 7.5 µl gamma-[^{32}P]-ATP (DuPont, Boston, MA, USA; 10 mCi/ml), 1.5 µl T4-polynucleotide kinase (Promega, Madison, WI, USA; 10 U/µl), 10 × buffer and H_2O], genomic DNA (1–2 µl containing 25–50 ng), deoxynucleosides triphosphate (GeneAmp dNTPs, Perkin Elmer, Branchburg, NJ, USA; 2 µl of a mixture containing 2 µg/ml of each of the 4 nucleosides), Taq polymerase (0.24 µl of 10 U/µl), 10 × buffer and H_2O. The PCR program consisted of 30 cycles of 1 min denaturing at 94°C, 1 min annealing at 55°C, and 1 min extension at 72°C. The reaction was stopped with 7 µl loading/stop buffer (formamide, 0.1% xylene cyanol, 0.1% bromophenol blue, and 2% 0.5 M EDTA).

Electrophoresis of the PCR products was carried out in acrylamide sequencing gels at 1800 V for 3 h. The gel was dried and exposed to film. Lod scores defined as logarithm to the base 10 of the ratio of odds in favor of linkage to the odds against linkage between RT70 and HIDS were calculated using the LINKAGE programs, assuming a recessive model of HIDS inheritance and a gene frequency of 0.001.

Statistical analysis. Statistical analysis was performed using the chi-squared method or Student's t test, indicated in Results.

RESULTS

Clinical analysis. The comparison of clinical manifestations of FMF and HIDS is shown in Table 1. The 2 diseases appear to be distinct in most aspects, including the duration of the attack, the temperature curve, the organs involved and the nature of the involvement, the response to treatment, and the prognosis. A typical attack of FMF lasts 2–4 days and is characterized by a temperature curve with a fast rise, plateau and abrupt fall, peritonitis, pleuritis or monoarthritis, possibly erysipelas-like eruption, and virtually no other dermal manifestations or lymphadenopathy (rarely, if ever, in children). On the other hand attacks of HIDS are marked by longer duration (around a week), gradual defervescence (lysis), common occurrence of lymphadenopathy and rash, and abdominal pain, which very infrequently develops into acute abdomen and symmetrical oligoarthritis or arthralgia. Amyloidosis, a life threatening manifestation of FMF, has not been noted in HIDS, and colchicine, while very effective in FMF, is less effective in HIDS. Additional dissimilarities exist, as outlined in Table 1.

Serological analysis. Results of Ig analysis in patients with FMF are presented in Tables 2–4. As shown in Tables 2 and 3, abnormally elevated levels of Ig of at least one isotype were noted in 34 of 70 patients (49%). Sixteen patients (23% of all patients and 47% of patients with increased Ig levels) had elevated IgA. Elevated IgM levels were noted in 9 patients (13%), IgG in 12 (17%), and IgD in 9 (13%). In 10 patients, the increased IgA level was associated with a concomitant rise of IgG (5 patients), IgD (4 patients), or IgD plus IgM (one patient). As a group, however, patients with FMF exhibited normal Ig levels between the attacks (Table 4, mean values in FMF).

All 9 patients with FMF (4 men and 5 women) who displayed elevated levels of IgD appeared to have classic FMF with attacks of peritonitis (9 patients), monoarthritis (7 patients), and pleuritis (3 patients), and had none of the specific HIDS clinical features delineated in the previous section. All were colchicine responsive and did not have skin manifestations or lymphadenopathy. Compared to patients with HIDS, patients with FMF had significantly lower rates of elevated individual Ig levels (Table 3), and significantly lower mean IgA and IgD levels (Table 4). Therefore, in addition to differences in IgD, the prevalence of elevated Ig levels and mean IgA levels also differentiate the disease.

Molecular analysis. A panel of 9 HIDS families was genotyped for the RT70 marker, which is about 1 cM centromeric to the FMF susceptibility gene on chromosome 16p. Lod scores between HIDS and RT70 are shown in Table 5. Total lod scores of < -2 were obtained up to recombination frequency of 0.03, excluding HIDS from the interval within 3 cM of RT70. Moreover, haplotype analysis, using RT70 typings in conjunction with 4 other markers[12], also rules out the placement of HIDS in the MEFV region of chromosome 16.

DISCUSSION

Although FMF and HIDS share certain features, we

Table 1. FMF and HIDS are clinically distinct.

Manifestation	FMF	HIDS
Age of onset	Usually before age 20	Childhood (70% before 1st year of life)
Duration of attack	1–4 days	3–7 days
Fever	Begins and ends abruptly. The temperature curve is of continuous type. Chills are common	Sudden rise. Gradual decrease. Chills are common
Abdominal attacks	Occur in most patients. Diffuse, or less frequently localized. Peritoneal irritation is the rule. Diarrhea is not common (5%)	Occurs in most patients; usually pain alone. Acute abdomen (in < 10%). Diarrhea very common (80%)
Joint attacks	Presents as monoarthritis of the large joints of lower extremities (75%). Polyarthralgia may occasionally accompany febrile attacks elsewhere. Chronic joints and spondyloarthropathy are rare (< 5% and < 1%, respectively)	Presents as symmetric oligoarthritis of large joints of lower extremities. Arthralgia is very frequent. No chronic joint disease found
Thoracic attacks	Pleuritis is common (25%), unilateral. Pericarditis is rare (< 1%)	Not found
Rash	Rare (< 5%). Only erysipeloid. Those affected experience only rare episodes during lifetime	Very common (90%). Types of rash: macular, maculopapular, purpura. Pathology: vasculitis
"Orchitis"	Rare (< 5%). Unilateral. Only in childhood and adolescence. Rare episodes during lifetime	Not found
Muscle pain	Short or prolonged episodes of febrile myalgia are uncommon. Afebrile muscle pain of lower extremities, usually provoked by exertion, is common (30%)	Rare
Lymphadenopathy	Questionable in early childhood	Generalized and cervical. Very common (> 90%)
Splenomegaly	In about 30% of patients	In about 50% of patients
Amyloidosis	Develops in many untreated patients	Not found
Vasculitis	Hypersensitivity, GN, PAN are more common compared to population not affected by FMF	Skin eruption
Genetic origins, populations	Autosomal recessive. The susceptibility gene is mapped to chromosome 16p. Sephardi Jews, Armenians, Arabs, and Turks	Autosomal recessive. Chromosomal location is not known. Occurs in Western Europeans
WBC in attack	Increased	Increased
ESR in attack	Increased	Increased
Hematuria	Common (5%)	Present in 20%
Synovial fluid	Turbid, inflammatory; white cell count > 20,000/μl	Turbid, inflammatory
Colchicine treatment	Prevents attacks and amyloidosis	Usually not effective

WBC: white blood cells; ESR: erythrocyte sedimentation rate; GN: glomerulonephritis; PAN: polyarteritis nodosa.

observed that the 2 diseases differ in their clinical manifestations, serum Ig concentrations, and genetics. Lymphadenopathy, certain types of rash, and symmetric oligoarthritis are exclusively found in HIDS, while peritonitis, monoarthritis, and pleuritis are typical to FMF (Table 1). Increased levels of IgG, IgM, IgA, and IgD have a much lower prevalence in FMF compared with prevalence reported in HIDS (Tables 2, 3, 4). Finally, molecular analysis,

Table 2. Patients with FMF with elevated immunoglobulin levels*.

Patient	Immunoglobulin Levels			
	IgG (6.5–15.2 g/l)	IgA (1.1–3.75 g/l)	IgM (0.5–2 g/l)	IgD (≤ 100 U/ml
3	**20.96**	1.23	2.0	20
6	14.18	2.63	**3.21**	< 5
7	12.47	**5.92**	2.0	57
8	14	**6.36**	1.46	80
9	**16.96**	1.74	**2.16**	51
11	9.06	**6.64**	1.48	**182**
13	9.86	2.75	**2.12**	28
14	**15.54**	1.89	0.94	54
15	**29.22**	**5.96**	1.91	17
16	13.87	2.42	2.0	**696**
18	13.25	2.42	**2.26**	60
19	11.65	**6.24**	1.07	17
21	12.08	1.77	**2.5**	58
23	**15.5**	3.68	1.58	38
27	15.08	**8.53**	0.76	60
29	**16.2**	**4.14**	1.98	3
35	15.08	**5.99**	1.66	**174**
36	11.1	1.28	**2.44**	19
37	**16.56**	1.68	0.61	19
38	14.4	**4.79**	1.92	**225**
41	8.6	**7.1**	1.42	**226**
43	**15.33**	3.34	0.98	59
48	13.29	**4.55**	**3.63**	**146**
49	10.32	**3.92**	0.66	10
55	12.15	**6.1**	2.0	52
57	**18.2**	2.99	1.93	45
58	**16.14**	**6.71**	0.48	44
60	13.3	3.79	0.8	**312**
61	12.3	3.67	0.57	**190**
62	15.20	3	**2.8**	**148**
64	9.5	2.89	**3.51**	64
65	**16.28**	**8.86**	0.86	73
67	**15.86**	**4.06**	1.98	4
70	15.19	3.70	1.98	49

*Ig levels were determined in 70 patients by nephelometry (IgG, A, M) and ELISA (IgD). Data are from patients with increased titers in at least one type of Ig (shown in boldface type).

Table 3. Prevalence of elevated immunoglobulins in FMF (70 patients) and HIDS (50 patients). Immunoglobulins were determined using nephelometry (IgG, IgA, IgM) or ELISA (IgD). Results for patients with FMF are shown in Table 2; for HIDS in reference[13].

Immunoglobulin	No. (%) of Patients		p*
	FMF	HIDS	
IgA	16 (23)	42 (82)	< 0.001
IgG	12 (17)	19 (38)	< 0.02
IgM	9 (13)	17 (34)	< 0.01
IgD	9 (13)	50 (100)	< 0.001
Any Ig	34 (49)	50 (100)	< 0.001

*Chi-squared test.

Table 4. Mean immunoglobulin levels in FMF (70 patients) and HIDS (50 patients). Immunoglobulins were determined using nephelometry (IgG, IgA, IgM) or ELISA (IgD). Mean Ig levels were computed based on Ig determination in sera of 70 patients with FMF (Table 2) and from reference[13] (50 patients with HIDS).

Immunoglobulin	Normal (g/l)	Mean Ig level		p*
		FMF	HIDS	
IgA	1.1–3.75	3.12	5.54	< 0.001
IgG	6.50–15.20	12.76	13.5	NS
IgM	0.50–2.00	1.47	1.42	NS
IgD	≤ 100 U/ml	57.22	1158	< 0.001

*Student's t test. NS: not significant.

Table 5. Linkage between RT70 and HIDS.

	Recombination Fraction						
	0.00	0.01	0.02	0.03	0.04	0.05	0.06
Lod score*	$-\infty$	−3.85	−2.72	−2.08	−1.65	−1.33	−1.08

*Lod scores of 9 families with one or more progeny with HIDS. Lod scores were computed using LINKAGE programs.

using the RT70 marker, confirmed that the HIDS locus is not linked to the FMF susceptibility gene on chromosome 16p (Table 5).

FMF and HIDS differ clinically in almost every aspect studied (Table 1). However, as some overlap does occur, recurrent painful febrile attacks may still constitute a diagnostic challenge. The clue for correct diagnosis is the presence of the pathognomonic manifestations outlined above. In addition, the origin of the patient is also helpful, as patients with HIDS and FMF stem from different populations (Table 1). Despite serologic characterization of HIDS and significant advancement toward the detection of MEFV, the diagnosis of the 2 conditions currently still relies on clinical evidence.

Genetic evidence also strongly supports the view that FMF and HIDS are distinct entities. That these diseases are common in different populations suggested a different genetic basis, although there remained the possibility that the 2 disorders could be allelic mutations at the same locus. However, our present data, coupled with the previous study from Drenth, *et al*[12], indicates that the HIDS susceptibility gene is not linked to the MEFV region of chromosome 16. The chromosomal location of the HIDS susceptibility locus remains unknown.

Studies focusing on Ig of various isotypes in FMF are scarce and report conflicting results. One study showed elevation of IgG, IgM, and IgA during attacks and remissions in untreated patients and in patients taking colchicine[20]. A study performed before the era of colchicine use found that only the IgG and IgM levels were invariably increased; the IgA levels were constantly low (reviewed in [20]). A third study showed normal IgG, IgM, and IgA in colchicine treated patients with FMF[21]. Our results agree with the latter, showing normal mean Ig levels in patients with FMF (Table 4), but also show that about half the patients may display an elevated level of Ig of one or more isotypes (Table 3). Differences with other studies may stem from variance in methodology. Our use of modern automated techniques of immunoglobulin determination, combined with our common experience of normal Ig levels obtained on multiple occasions, supports our results.

Our findings have an important consequence: while virtually all patients with HIDS display high concentrations of IgD[11,13], the opposite is not true; the finding of elevated levels of IgD in a patient with periodic fever is not necessarily diagnostic of HIDS. About 13% of our patients with FMF had elevated IgD titers, half of them with levels higher than twice the normal upper limit (> 200 U/ml, Table 2). The reason for increased IgD in 13% of patients with FMF is not clear. None of these patients with FMF had specific manifestations of HIDS. In the normal population IgD has a trimodal distribution pattern with a 95% confidence interval from 0.19 to 156 U/ml[22]. It is possible that the high IgD values in some patients with FMF reflect the high end of the normal distribution.

The finding that IgA levels are elevated in a considerable number of patients with FMF is novel and interesting: FMF has been associated with increased prevalence of Henoch-Schönlein purpura and IgA nephropathy[23,24], conditions associated with deposition of IgA in the affected tissues[24,25]. FMF is also associated with increased prevalence of spondyloarthropathy[26], in which raised IgA was found to correlate with disease activity and was linked to bacterial infection of the gut[27]. The role of increased IgA level in FMF and its association with certain immunologic and rheumatologic manifestations of the disease is intriguing and is currently being investigated.

The results of the clinical, serological, and genetic analysis in this study suggest that FMF and HIDS are 2 separate diseases, differing in their molecular basis, pathogenesis, clinical expression, response to treatment, and prognosis. How these 2 different entities share common features, such as an episodic nature and certain system and organ involvement, remains to be elucidated.

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