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HYPERIMMUNOGLOBULINAEMIA D AND PERIODIC FEVER: A NEW SYNDROME

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Summary Six patients of Dutch ancestry with a long history of recurrent attacks of fever of unknown cause were found to have a high serum IgD level and a large number of plasma cells with cytoplasmic IgD in the bone marrow. Because the clinical picture in some ways resembled that of familial Mediterranean fever (FMF), sera of patients with FMF were also investigated; only one of eight such patients had a raised serum IgD.

Introduction

RECURRENT fever often presents a diagnostic puzzle, and in a few patients even the most elaborate techniques yield no answer. This is true of familial Mediterranean fever (FMF), in which diagnosis on clinical grounds may take a long time—even in patients of Jewish, Armenian, or Arab ancestry.¹⁻³ Lately we have seen six patients with a long history of recurrent fever of unknown cause. The syndrome was reminiscent of FMF but differed from it in several respects.

Patients and Methods

All the patients were interviewed and examined repeatedly by at least one of us. The results of investigations done in our hospital and

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other hospitals were reviewed. The clinical features are summarised in table 1. The following items are of special interest:

1. All patients had a long history of recurrent fever and were undiagnosed despite repeated thorough clinical and laboratory investigation. Tuberculosis, brucellosis, recurrent cytomegalovirus infection, and persistent Epstein-Barr virus infection were ruled out.

2. A precipitating event for the attacks has usually been absent, but some patients have premonitory symptoms such as headache.

3. High fever ($>39^{\circ}\text{C}$), usually preceded by chills, is the main feature of an attack. Among the accompanying signs and symptoms, headache and swollen lymph nodes are prominent. (FMF patients usually do not show lymphadenopathy.¹⁻³) Leucocytosis ($10-20 \times 10^9/l$) is commonly present during attacks.

4. Abdominal complaints seem to be less frequent and less severe than in FMF.^{1,2} Two of the patients had had an appendectomy. No information could be obtained about the appendectomy in patient 2, but patient 3 had been operated on because of abdominal pain, presumably not associated with the periodic fever; on section the appendix showed no acute inflammation but there were signs of earlier inflammation. Serositis, a prominent feature of FMF, was not identified in any of our patients. In patients 1, 5, and 6 diarrhoea occasionally coincided with the attacks. (Diarrhoea is not prominent in FMF—indeed, FMF patients are often constipated during attacks.¹)

5. None of our patients has shown fixed periodicity of the attacks, and in our female patients the attacks have not been associated with the menstrual cycle. The frequency of attacks varies considerably in most of our patients, some of them having symptom-free phases of several months.

6. All six patients are of Dutch ancestry, and none is known to have Jewish, Armenian, Arab, or other Mediterranean relatives. Three patients had a positive family history. The mother of patient 5 had had the same disease, dying of secondary amyloidosis. Two of the mother's brothers also had periodic fever, one of them also with amyloidosis (see below).

7. Four of the six patients are being treated with colchicine. Because of his low attack rate, patient 5 was advised to take

TABLE I—CLINICAL FEATURES OF PATIENTS 1-6

Patient	Age (yr)/sex	Age at onset (yr)	Signs and symptoms associated with an attack								Duration of attacks (days)	Frequency of attacks (/yr)*	Family history	Response to colchicine	
			Fever	Chills	Headache	Swollen lymph nodes	Abdominal pain	Rash	Arthralgia	Splenomegaly					
1	18/M	4	+	+	+	+	+	+	(+)	(+)	(+)	4	6-8	Brother of patient 2	Remission
2	31/F	1	+	+	(+)	+	(+)	-	-	+	-	5	6	Sister of patient 1	Remission
3	17/M	12	+	+	+	-	(+)	-	-	-	-	1-2	≥12	Negative	Remission
4	30/F	?	+	-	-	+	-	-	-	-	-	2	12	Negative	Not treated
5	14/M	8	+	+	+	-	+	-	-	-	-	2-5	2	Positive†	Follow-up too short
6	20/F	1	+	+	+	+	(+)	+	-	-	-	5	10	Negative	Remission on high dose

*Before colchicine.

†Mother and 2 maternal uncles (see text).

TABLE II—FEATURES OF PATIENTS WITH TRUE FMF

Patient	Age (yr)/sex	Country of origin	Manifestations during attacks				Colchicine	Serum IgD (IU/l)*
			Abdominal	Thoracic	Articular	Fever		
A	48/M	India			+	+	On demand	<14
B	43/M	Jordan	+	(+)	(+)	+	Continuous	<14
C	23/M	Turkey		+		+	No	<14
D	60/M	Turkey		(+)		+	On demand	<14
E	10/F	Turkey	+	+		+	Continuous†	77
F	5/F	Turkey	+			+	Continuous†	28
G	16/F	Turkey	(+)	+	(+)	+	Continuous†	177
H	32/M	Turkey	+		+	+	Continuous	71

*Normal <150 IU/l.

†Patient compliance questionable.

colchicine as soon as he experienced prodromal symptoms. Patients 1 and 3 were also advised to take colchicine on demand after it had been shown to prevent attacks.

Case-history

The case-history of patient 6 is presented in more detail to illustrate the syndrome. This patient was born in 1961. When she was a baby high fever developed after vaccination for measles. Since 1962 she has had bouts of fever about once a month, preceded by chills and accompanied by abdominal pain, diarrhoea, and swelling of lymph nodes. In 1964 a tonsillectomy was performed. Because of occasional leucocyturia and erythrocyturia she had a urological investigation, but no diagnosis was reached. In 1970, 1972, 1973, 1976, 1979, and 1981 extensive clinical investigations failed to reveal any definitive microbiological or immunological abnormality, although some weight was assigned to the finding of salmonella in the faeces (in 1979) and to one isolated positive blood culture with a "viridans" streptococcus (contamination?) in 1981. Salicylates seemed to have some favourable effect. Immunisation against tetanus provoked an episode of fever. In recent years the character of the attacks has changed, in that abdominal pain and diarrhoea are no longer prominent symptoms. In a typical attack she has gradually increasing weakness, with some lightheadedness and nasal congestion, followed by chills and a rapid rise of body temperature. The cervical lymph nodes become tender and she cannot tolerate anyone in her vicinity. These episodes last an average of 5 days, during which virtually no food is taken.

When we first saw this patient in 1981, we assumed that she had the same disease as the other patients in the series. She was treated with colchicine, 1 mg a day, and the frequency and severity of the attacks decreased. During one of the attacks a painful rash appeared transiently on the distal parts of the legs and the arms. Biopsy specimens were taken (see below). In the same period some erythrocyte casts were found in the urine.

Laboratory Methods

Immunoglobulins.—Immunoglobulin studies were performed on fresh serum samples (ie, within 48 h of venepuncture), or on sera stored at -20°C after addition of epsilon-aminocaproic acid (final concentration 0.5%) to prevent "spontaneous" degradation of IgD.^{5,6} All serum samples were investigated by agar electrophoresis (method of Wieme⁷) and by immunoelectrophoresis with a rabbit antiserum recognising all immunoglobulin isotypes (RAHu Ig [GAMD], Nordic Immunological Laboratories, Tilburg, The Netherlands). In addition, sera from three patients were investigated by immunoselection to assess the heterogeneity and the light chain type composition of IgD.⁸ Immunoglobulins of individual isotypes were quantified by single radial immunodiffusion (modification of the method of Voormolen-Kalova et al⁹), monospecific antisera being prepared as described elsewhere.¹⁰ Immunofluorescence studies to investigate cells containing cytoplasmic immunoglobulins were performed in bone marrow preparations by the method of Hijmans et al.¹¹ Immunoglobulin-containing cells in biopsy specimens of other tissues (lymph nodes, skin) were investigated by immunofluorescence and immunoperoxidase techniques described elsewhere.¹²

Immune-complex assay and complement determinations.—The ¹²⁵I-Clq binding assay (ClqBA) was performed by the method of Zubler et al.¹³ Complement levels (Clq, C4, and C3) were determined by radial immunodiffusion and CH50 levels.¹⁴

Lymphocyte transformation tests.—The proliferative response in vitro of peripheral blood lymphocytes after stimulation with mitogens (phytohaemagglutinin, pokeweed mitogen, antilymphocyte serum, and concanavalin A) and antigens (tetanus toxoid, diphtheria toxoid, and a cocktail of mumps, varidase, candida, trichophyton, and purified protein derivative) was assessed

TABLE III—IMMUNOGLOBULINS IN PATIENTS 1–6

Patient	Serum immunoglobulins (IU/l)					Bone-marrow plasma cells containing cytoplasmic immunoglobulins (%)					
	IgG	IgM	IgA	IgD	IgE	γ	μ	α	δ	κ/λ ratio of IgD	κ/λ ratio of total Ig
1	74	78	246	674	<100	30	4	38	28	78/23	68/32
2	234	71	239	1383	<100	37	2	26	36	59/41	57/43
3*	62	162	96	193	<100	17	14	33	36	ND	53/47
4	134	211	239	434	<100	ND	ND	ND	ND	ND	ND
5	95	105	199	196	<100	43	11	34	12	ND	ND
6	70	90	220	5300	<100	2	1	17	81	76/24	77/23
Normal range	65–200	45–335	65–200	<150	<100						
Mean \pm SD†						51 \pm 11	9 \pm 8	36 \pm 10	4 \pm 8	ND	56 \pm 7/44 \pm 7

*In 1979, serum IgD was 64. Immunoglobulin values were determined in serum collected in 1983; bone-marrow fluorescence studies were performed in 1979.

†In 33 normal bone-marrow specimens.

ND=not done.

in the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (Dr P. Th. A. Schellekens) as described elsewhere.¹⁵

Phagocyte function tests.—Phagocytosis and intracellular killing of *Staphylococcus aureus* by granulocytes and monocytes were assessed by the method of van Furth et al.¹⁶

Classic FMF Patients

For comparison, eight patients with true FMF were tested for IgD. Their clinical manifestations are summarised in table II. The case-history of patient B has been reported elsewhere.¹⁷ For one patient (A), serum samples taken before and during colchicine therapy were available. Bone marrow from this patient was studied for cells containing cytoplasmic immunoglobulins.

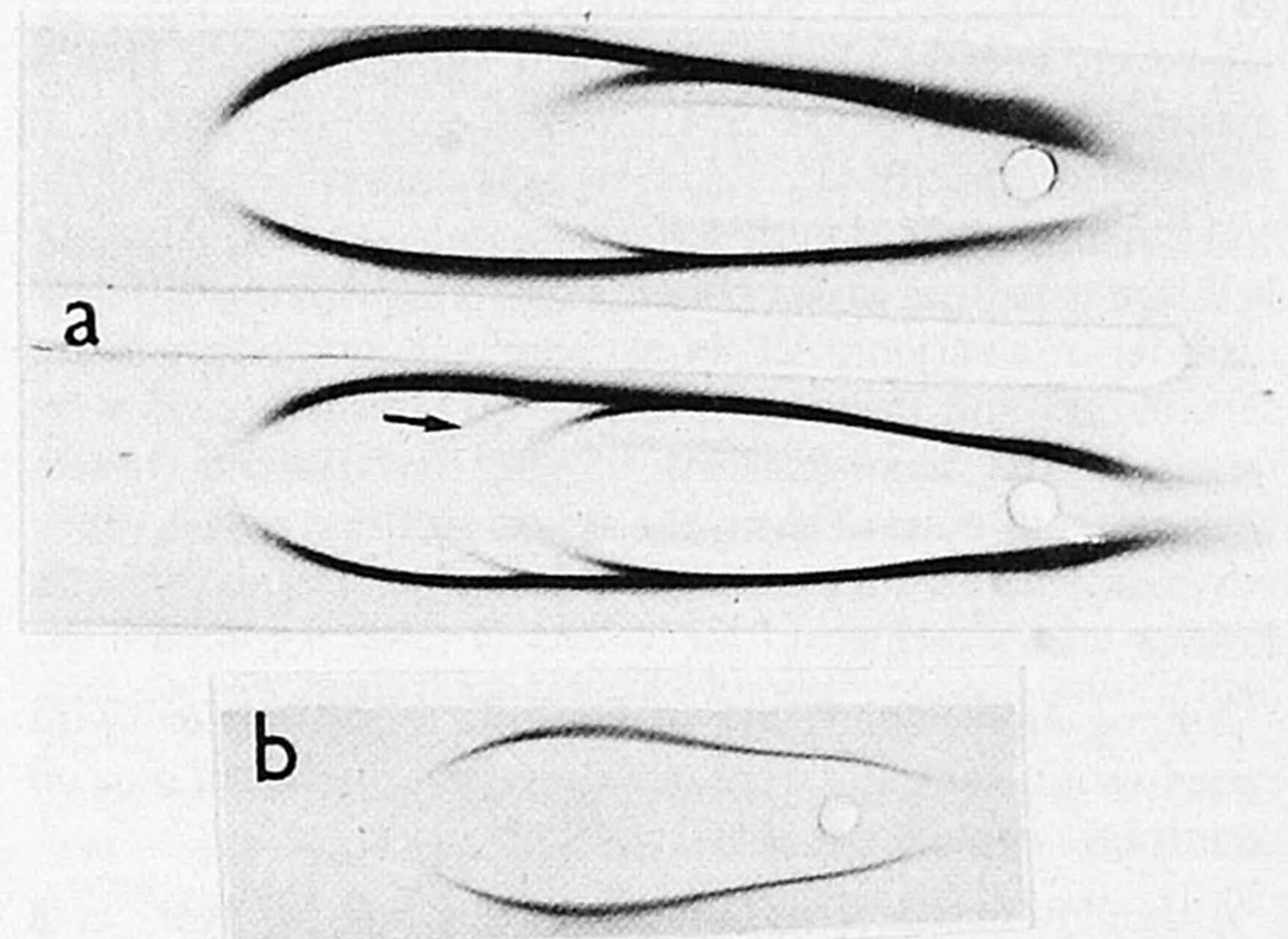
Results

All six patients had a raised serum IgD (table III). In addition, patients 1, 2, and 4 had a slightly increased IgA and patient 3 a mildly depressed IgG. In patient 3 the serum IgD at first admission (1979) was 64 IU/ml, which is in the upper range of normal, whereas a recent specimen showed 193 IU/ml (table III).

An example of the serum Ig pattern (patient 6) is shown in the accompanying figure. None of the patients had any indication of paraproteinaemia: no homogeneous Ig component was found on agar electrophoresis and in all the serum samples tested by immunoelectrophoresis the IgD precipitin line was asymmetrical (ie, heterogeneous). In the three cases investigated the immunoselection technique showed a strikingly raised concentration of heterogeneous IgD composed of both κ and λ light chain types in about equal parts. Except in patient 3 (see above), there was little fluctuation of serum IgD; the concentrations did not rise or fall during attacks of fever and were not influenced by colchicine treatment.

Sera from two brothers of the mother of patient 5, both of whom had periodic fever, were kindly sent to us by Dr M. H. van Rijswijk (University Hospital, Groningen). In the serum of one of these patients, who has been treated with colchicine since 1977, the IgD concentration was at the upper limit of normal (99 IU/l). His brother, who has been free of attacks since renal transplantation for renal amyloidosis in 1979, has a normal serum IgD (4 IU/l).

The IgD content of the sera of eight FMF patients was also investigated (table II). In five of these patients the serum IgD level was low, in two it lay at the upper limit of normal, and in one patient it was clearly raised.



Serum immunoelectrophoresis pattern in patient 6.

(a) Comparison with normal human serum (upper pherogram). Note extra precipitin line in patient's serum (middle pherogram) between IgG and IgA (arrow). (b) The line (lower pherogram) represents a high level of IgD (antisera from Nordic Immunological Laboratories).

Plasma cells containing cytoplasmic immunoglobulins were investigated in bone-marrow samples from five of our non-Mediterranean patients. The percentage of delta-positive cells was abnormally high in all (table III), whereas bone marrow from FMF patient A had only 0.2% delta-positive cells.

Lymph-node biopsy specimens were taken in patients 1, 2, and 3. In patient 1, a lymph node with hyperplasia of the B cell system was found and many plasma cells were positive for either IgD or IgA. The lymph node of patient 2 showed many plasma cells containing IgD or IgM. The lymph node of patient 3 showed many plasma cells containing IgA, few with IgG and IgM.

The skin biopsy specimen taken from patient 6 during an attack (see above) showed lymphocytic vasculitis with mononuclear infiltrates around vessels high and deep in the dermis, swelling of the endothelium, extravasation of erythrocytes, and nuclear detritus. Locally, there was mononuclear cell infiltration of the vessel wall. Immunofluorescence studies showed perivascular depositions of IgA and C3 but no IgD.

The ClqBA was positive only in patient 6. With this method, circulating immune complexes were invariably present, whether before, during, or after a febrile attack. Complement levels were normal except in patient 3, who had

low CH50 and Clq during an attack, and in patient 6, who had a low Clq level both during and after an attack (which indicates complement activation via the classic pathway).

Lymphocyte transformation tests in patients 1, 3, 5, and 6 gave normal results for both mitogens and antigens. Phagocytosis and intracellular killing of *Staphylococcus aureus* by granulocytes and monocytes, assessed in all patients, were normal.

Discussion

The clinical picture in these patients resembles that of FMF. This is exemplified by the positive family history in patients 1, 2, and 5, the secondary amyloidosis in the family of patient 5, the periodic fever, the blood leucocytosis during an attack, and the response to colchicine. The painful skin lesions below the knees in patient 6 were remarkably similar to the erysipelas-like skin lesions described in FMF.^{1,2,18} However, several of the signs and symptoms are clearly dissimilar from those in FMF. Lymphadenopathy is extremely rare in FMF,¹⁻³ and serositis, prominent in FMF, was not encountered with certainty in our patients. Also, the IgD abnormalities in our patients seem to indicate a different disorder or a variant. All six patients had a strikingly raised serum IgD and large numbers of IgD-positive cells were found in the bone marrow of the five patients tested. Moreover, in most of them the serum IgA was raised, albeit not greatly. In all but patient 3, serum IgD changed little with time or with treatment.

Among eight classic FMF patients, we found only one with raised serum IgD. We were unable to find published data on serum IgD in such patients.

Although much is known about the role of IgD, as a membrane-bound immunoglobulin, in the regulation of the immune response, the function of IgD in the serum is not clear.^{19,20} The concentration range in a normal population is wide and has a bimodal or trimodal distribution^{21,22} that has been ascribed to differences in rate of synthesis.²³ Low IgD concentrations are commonly seen in normal individuals and are genetically determined.²⁴⁻²⁶ Slightly increased concentrations have been observed in cigarette smokers²⁷ and greatly increased concentrations in patients with recurrent bacterial infections^{28,29} and immunodeficiency (such as the hyper-IgE syndrome²²). Few workers have been able to demonstrate antibody activity within the IgD class,³⁰⁻³³ and the physiological role of such antibodies is obscure.

It is tempting to speculate about the role played by IgD in the pathogenesis of the periodic fever seen in our patients. For example, these patients might be more apt to produce IgD for some genetic reason. Contact with various antigens might lead to formation of IgD complexes capable of triggering macrophages to produce interleukin 1, the endogenous pyrogen, which would induce fever. An immune-complex mechanism would be consistent with the signs and symptoms associated with the attacks. In patient 6 the cutaneous vasculitis as well as the signs of glomerulonephritis during an attack support the notion of an immune-complex pathogenesis, as does the detection of circulating immune complexes in the Clq-binding assay. These could conceivably be IgD complexes, which can also lead to complement activation.³⁴ The failure to detect IgD in the skin biopsy specimen may have been due to the instability of this immunoglobulin⁵ and further investigations are clearly needed.

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