Journal of Clinical Immunology, Vol. 9, No. 5, 1989

Clinical and Immunological Studies in Patients with an Increased Serum IgD Level

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Accepted: June 12, 1989

Increased levels of serum IgD can be found in single patients with a variety of clinical syndromes and in the disease entity designated hyper-IgD syndrome which is associated with periodic fever and lymphadenopathy. We investigated 17 patients, both children and adults, with high serum IgD levels ranging from 220 to 5300 IU/ml. Eight patients had periodic fever and lymphadenopathy, four showed a humoral immunodeficiency, and the remainder had a variety of clinical abnormalities. Serum IgA levels were consistently high in all patients except in those with an immunodeficiency. Serum IgD complexes were detectable in each serum, which indicates that the occurrence is not pathognomic for the syndrome of periodic fever. Antibody formation against the primary antigen *Helix pomatia* hemocyanine and the secondary antigen tetanus toxoid showed no abnormalities in the patients without an immunodeficiency. Bone marrow origin of serum IgD was strongly suggested by enumeration of IgD-containing plasma cells. We conclude that no apparent relationship exists between the several clinical syndromes and increased serum IgD.

KEY WORDS: Serum IgD; periodic fever; immunodeficiency; immune status.

INTRODUCTION

The function of the human immunoglobulin isotype IgD, as identified in 1964 by Rowe and Fahey (1), is still not completely solved. The IgD molecule occurs as membrane-bound protein on lymphocytes of B-cell lineage and also in serum and other body fluids. Membrane-bound IgD probably plays a role in antigen-triggered B-lymphocyte differentiation (2, 3). Although antibody activity can be detected in soluble serum IgD, its role in the defense against infections is less clear since effector functions such as binding to phagocytes are lacking (4, 5).

IgD comprises about 1% of the total serum immunoglobulin pool in man. The concentration in serum as measured in healthy infants and adults is age dependent and shows a considerable biological variation within people of the same age (1, 6, 7). Serum IgD levels of a population are not normally distributed (7). Dunette *et al.* (8) showed in a study of 300 individuals aged 6 to 18 years that about 14% of the individuals had an extremely low serum IgD. The latter phenomenon appeared to be genetically determined, in that an autosomal recessive pattern of inheritance and an HLA association were described (8, 9). In contrast, a substantial number of healthy individuals showed an increased serum IgD level (1, 7, 8; unpublished observations of Out, Vossen, and Zegers), but a discernible inheritance pattern or HLA association was not demonstrable (8).

The role of serum IgD in disease is not clear. Increased serum IgD levels are found in patients with various types of immunodeficiency diseases, in patients with severe recurrent infections of the respiratory tract, and in single patients with a variety of clinical syndromes or abnormalities (10). Recently a clinical disease entity has been described, designated the hyper-IgD syndrome, which is characterized by periodic fever and lymphadenopathy associated with strongly increased levels of serum IgD of up to 6000 IU/ml serum (11).

Since we were interested in the role of serum IgD in disease a multicenter study was designed aimed

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0271-9142/89/0900-0393$06.00/0

to analyze the clinical and immunological findings in a series of patients with a variety of diagnoses and with high serum IgD levels which were under the care of the members of the Dutch Working Group for Immunodeficiencies. The main criterion for entry in the study was a level of serum IgD equal or higher than 150 IU/ml as determined on two occasions with an interval of at least 1 month.

PATIENTS AND METHODS

Patients were entered into this multicenter study after informed consent was obtained. The entry criterion was a serum IgD level higher than 150 IU/ml on two occasions at least 1 month apart. Included were 6 adults and 11 children; age varied between 3 and 60 years.

The data were collected according to a protocol written by the Dutch Working Group for Immunodeficiencies (see Table I).

With respect to the history of the patient and his/her family, special attention was paid to infectious diseases, recurrent fever, vaccination sequela, allergic symptoms, malignancy, autoimmune diseases, tonsillectomy, adenotomy, and appendectomy.

White blood-cell count, total lymphocyte counts, routine urine analysis, serum autoantibodies such as antibodies against erythrocytes, antinuclear antibodies, anti-double-stranded DNA, rheumatoid factors, and serum immunoglobulin (Ig) levels were determined by standard methods.

Table I. Protocol Design

	Time (days)							
	0	14	21	35	63	120	240	360
Physical examination, routine laboratory[a]	x							
Tetanus toxoid booster	x							
Tetanus toxoid antibodies	x	x						
HPH immunization			x					
HPH antibodies			x	x	x			
Serum IgD levels	x					x	x	x
Bone marrow		x						
Cellular immunity[b]		x		x				

[a]White blood-cell count, total lymphocyte count, urine analysis, serum autoantibodies, serum immunoglobulin levels, and saliva collection.

[b]Circulating B- and T-cell numbers and *in vitro* proliferative responses of lymphocytes to mitogens, antigens, and allogeneic cells.

Saliva was collected during 15 min according to Lourie (12). The first specimen was discarded; in the second specimen IgM, IgG, IgA, and IgD levels were measured (13, 14).

IgD complexes were determined by Dr. M. R. Daha (Leiden) in serum that had been immediately frozen at −70°C. After precipitation with polyethyleneglycol 6000 (final concentration, 3.5%), high molecular weight IgD (presumably IgD complexes) was measured with a radioimmunoassay using monoclonal anti-IgD antibody; results are expressed as the percentage of a positive control serum containing 739 ng IgD complexes/ml.

Patients were immunized with the secondary antigen tetanus toxoid and specific antibodies in the IgG and IgD class before and after immunization were measured by an enzyme-linked immunosorbent assay (ELISA) (15). Immunization with 1 mg of the primary antigen *Helix pomatia* haemocyanin (HPH) was performed subcutaneously in the deltoid region, and class-specific antibody levels (IgM, IgG, IgA, and IgD) were measured by an ELISA in serum obtained before and 14 and 42 days after immunization; HPH antibodies were expressed as a percentage of a positive reference sample as described (16).

In vitro proliferative responses of peripheral blood mononuclear cells to the mitogens phytohemagglutinin (PHA), pokeweed mitogen (PWM), and concanavalin A (Con A), to the antigens tetanus toxoid, *Candida albicans*, and HPH, and to allogeneic cells were determined with standard methods.

Circulating B cells were enumerated as surface Ig-positive cells and μ and δ expression was determined as described (17). T-cell numbers were determined using the monoclonal antibody OKT3 (CD3) (Ortho Pharmaceuticals, Raritan , NJ).

Bone marrow specimens were analyzed for plasma cells by cytoplasmic immunofluorescence for IgM, IgG, IgA, and IgD (18). Also, combined staining for the presence of surface IgM (sIgM) and sIgD on small cytoplasmic IgM (cIgM)-positive cells, on large cIgM-positive, and on large cIgD-positive cells was performed.

RESULTS

Clinical findings and levels of serum IgM, IgG, IgA, IgD, and IgE are presented in Table II. All 17 patients had an elevated serum IgD (range, 175–5300 IU/ml). Patients 1 to 8 suffered from a syndrome characterized by periodic fever from the age

Table II. Survey of the Clinical Data of the Patients and the Levels of Serum IgM, IgG, IgA, IgD, and IgE[a]

Patient No.	Age	Sex	Diagnosis	IgM (g/L)	IgG (g/L)	IgA (g/L)	IgD (IU/ml)	IgE (IU/ml)
1	10	♀	Periodic fever	1.56	14.1	*3.3*	*312*	16
2	10	♂	Periodic fever	1.02	*16.1*	*3.3*	*1450*	<100
3	10	♂	Periodic fever	0.93	*16.3*	*6.3*	*1180*	5
4	7	♀	Periodic fever	0.45	9.3	*2.1*	*3250*	23
5	20	♀	Periodic fever	0.77	*5.6*	*3.1*	*5300*	<100
6	35	♀	Periodic fever	1.2	9.6	2.6	*1068*	12
7	6	♂	Periodic fever	0.95	7.2	*3.2*	*2813*	42
8	16	♂	Periodic fever	0.99	11.3	*3.3*	*175*	40
9	4	♂	Heiner syndrome	0.98	*15.1*	1.3	*198*	*1500*
10	17	♂	Hay fever	1.88	15.0	2.7	*262*	*450*
11	3	♂	Bronchiectasis	1.19	*28.1*	*4.2*	*1800*	*414*
12	10	♂	Postinfectious arthritis	1.8	11.5	*2.5*	*220*	154
13	60	♂	Rheumatoid arthritis	1.0	*25.7*	*7.8*	*636*	*2300*
14	23	♂	XLA	*0*	9.6	*0*	*318*	9
15	27	♂	XLA	*Trace*	5.8–7.0	*0*	*190*	<1
16	17	♂	CVID	0.88	*3.7*	*0.04*	*191*	2
17	40	♂	IgM deficiency	*<0.3*	9.9	*3.2*	*316*	<1
18	14	♂	Healthy control	1.17	8.2	1.8	64	*1200*

[a]The italicized data of the serum immunoglobulin levels indicate a deviation of the normal level. For IgM, IgG, IgA, and IgD the levels from Ref. 13 are used; for IgE, Ref. 19.

of 4 months onward. The fever recurs every 1 to 2 months; an episode lasts 2 to 3 days and is sometimes accompanied by an erysipelas-like rash, cervical lymphadenopathy, abdominal pain, and arthritis. No viral causes have been identified (except patient 2, who suffers from a persistent Epstein–Barr virus infection). Clinically the syndrome of periodic fever resembles, to some extent, familial Mediterranean fever (FMF) but the response to colchicine is equivocal. In patient 2 a hypoallergenic diet seems to be successful (personal communication of Dr. R. S. Weening). Patients 3 and 4 are siblings from healthy nonconsanguinous parents. Patients 5, 6, and 8 have been described earlier (11). The illness of patient 8 (see Ref. 11) resembles FMF very much; his response to colchicine is favorable, and his mother and maternal uncle suffered from the same syndrome complicated by renal amyloidosis. In patient 9 the diagnosis of Heiner syndrome, i.e., pulmonary hemosiderosis and cow's milk allergy, was made. Patient 10 has allergic pollinosis. He became donor of a bone marrow transplant to his HLA-identical brother, who suffered from acute leukemia. Although serum immunoglobulins in the recipient have reached normal values after transplantation, no increase in serum IgD is seen. Patient 11 showed bronchiectasis of unknown etiology and patient 12 presented with transient arthritis after infection. Patient 13 had rheumatoid arthritis associated with polyclonal gammapathy.

Patients 14–17 have various types of humoral immunodeficiency syndromes. The serum immunoglobulin values of patient 16 date from before γ-globulin substitution; the others were investigated while on substitution therapy. Serum IgG was increased in several patients; serum IgG subclass levels were not deficient (data not shown). IgM was normal except for the patients with the immunodeficiency syndromes. Remarkably there was an increase in serum IgA levels in almost every patient. Serum IgE was increased in four patients, Nos. 9, 10, 11, and 13; all but one have pulmonary problems. There was no correlation between IgE and IgD serum levels.

Table III shows the levels of immunoglobulins in saliva. The results show that IgD was increased in only 4 of 10 patients, and secretory IgA in 2 of 10.

The results of analysis of serum IgD complexes showed the presence of polyethylene glycol-precipitable IgD in each sample investigated. A remarkable, linear correlation was detected between the serum IgD level and serum IgD complexes ($r = 0.87$; Fig. 1). When the polyethyleneglycol precipitates from three sera were analyzed by gel filtration on Sephacryl S300, the samples contained anti-IgD-reactive material with molecular weights higher than 300 kD, suggesting the occurrence of either aggregated IgD or IgD in immune complex form.

Table III. Saliva IgM, IgG, IgA, and IgD Levels[a]

Patient	Age	Sex	IgM (mg/L)	IgG (mg/L)	IgA (mg/L)	IgD (IU/ml)
1	10	♀	*4.1*	*3.1*	*97.9*	*0.13*
7	6	♀	0.9	<0.4	21.2	0.06
8	16	♂	<0.4	<0.4	5.5	<0.02
9	4	♂	0.75	0.5	30.6	<0.02
10	17	♂	<0.4	<0.4	78.5	<0.02
13	60	♂	<0.4	<0.4	2.9	<0.02
14	23	♂	n.d.[b]	n.d.	5.4	*0.98*
15	27	♂	<0.4	*6.0*	0.7	*0.30*
16	17	♂	*7.5*	*41.0*	21.7	*1.48*
17	40	♂	<0.4	<0.4	*101.3*	0.04
18	14	♂	0.5	0.4	31.0	<0.02
Control values[c]			1.01[c] (0.76)	<0.3[c]	44.2[c] (32.8)	<0.02

[a]The italicized data indicate a deviation of the normal level.
[b]Not done.
[c]Reference 14; mean (SD); $N = 9$; age, 10–24 years.

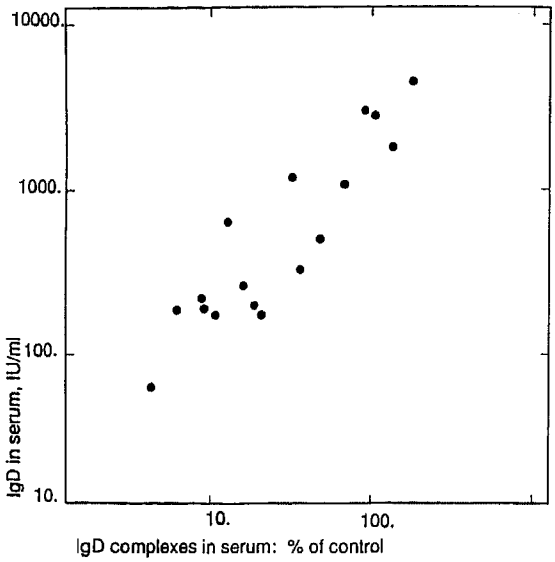

Fig. 1. Correlation between the serum level of IgD and the quantity of IgD complexes.

After immunization with the primary antigen *Helix pomatia* hemocyanine (HPH) the IgM-, IgG-, and IgA-class antibody response in several patients is below that seen in normal adults (Fig. 2). Compared to age-matched controls (20) the HPH antibody response is completely normal. Patients 14–17, having a humoral immunodeficiency, all showed no response following HPH immunization and those results are not included in Fig. 2. Five of 15 patients show detectable anti-HPH responses in the IgD class. Booster immunization with the secondary antigen tetanus toxoid showed a significant rise in antitetanus antibodies in all patients except for the immunodeficient patients. The range of the ratios between the post- and the preimmunization titers of the patients did not differ significantly from that in controls. In patients 1, 8 and 13 and in the control, 18, an antibody response to tetanus toxoid in the IgD class was demonstrable. Only one of these patients showed an anti-HPH response of the IgD class. In patients with periodic fever the immunization with tetanus toxoid induced a classical attack (11). In contrast hemocyanine immunization

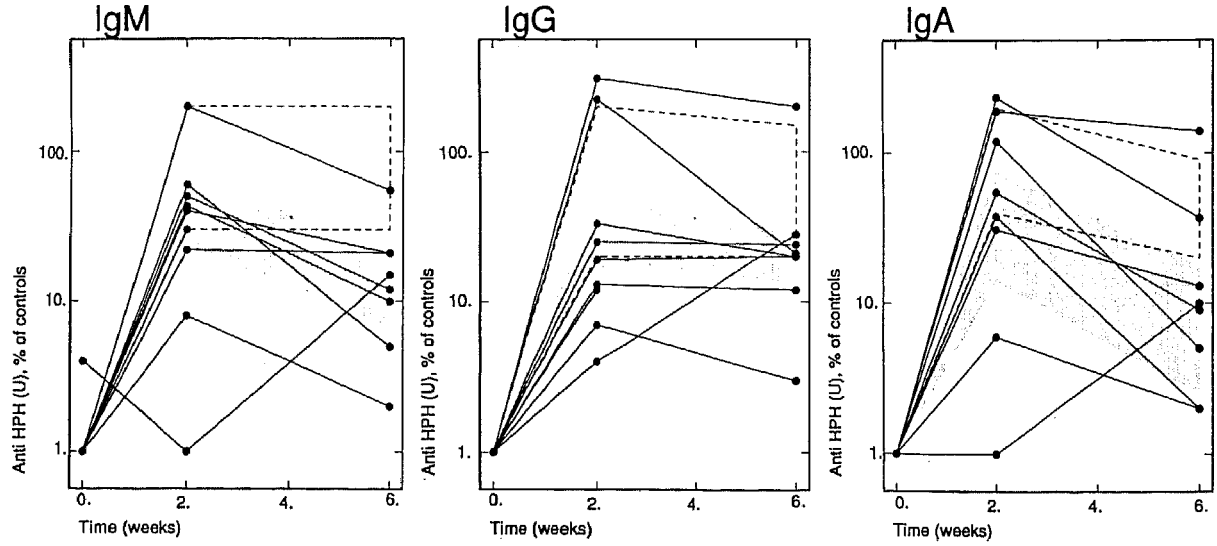

Fig. 2. Antibody formation against *Helix pomatia* hemocyanine in patients with increased serum IgD. Areas between dashed lines represent measurements ± 1 SD obtained in 14 normal adult controls (16). Stippled areas represent the results obtained in age-matched normal children (20).

Table IV. Analysis of Cells of the B Lineage in Bone Marrow[a]

(A) Ig-containing cells/10^5 lymphocytes and plasma cells

Patient No.	Age	Diagnosis	cIgM	cIgG	cIgA	cIgD
1	10	pf	*469*	*1856*	*1048*	*928*
2	10	pf	108	*624*	401	*924*
3	10	pf	125	*1117*	*2921*	*5128*
4	7	pf	*51*	*491*	448	*1383*
5	20	pf	*30*	79	*876*	*4145*
6	35	pf	104	721	567	*1668*
7	6	pf	134	*428*	323	*1988*
8	16	pf	262	*999*	*794*	*287*
9	4	Heiner syndrome	99	*899*	*392*	*309*
10	17	Hay fever	*491*	626	856	*964*
13	60	r.a.	*53*	*793	*517*	*405*
14	23	XLA	*0*	*33*	*0*	85
15	27	XLA	*54*	*229*	*0*	*373*
16	17	CVID	*645*	*16*	*0*	*629*
17	45	IgM deficiency	*276*	*1734*	*2071*	*883*
18	14	Control	156	*621*	374	56
Control values[b]						
2–6 healthy			34–203	35–268	49–348	0–29
6–15 healthy			25–235	42–403	39–444	0–103
Adult healthy			99–257	318–1331	247–1372	5–204

(B) Surface IgM and surface IgD on IgM- and IgD-containing cells

	On small cIgM+[c]		On large cIgM+[d]		On (large) cIgD+	
Patient No.	% sIgM	% sIgD	% sIgM	% sIgD	% sIgM	% sIgD
1	69	43	67	1	20	93
2	65	65	88	39	70	76
3	74	68	26[e]	5[e]	22	59
4	42	34	49	15	7	77
5	100	66	81	71	0.2	91
6	67	62	76.5	26	37	85
7	39	16	62[e]	40[e]	10	98
8	59	42	86	33	46	90
9	51	20	80	12	0	69
10	58	41	46	6	7	94
13	82	76	92[e]	25[e]	16	94
14	16	2	No large cIgM+		0[e]	64[e]
15	No small cIgM+		No large cIgM+		2	85
16	Not done		Not done		Not done	
17	53	40	45	60	2	89
18	71	57	93	56	80	100

[a]The italicized data indicate a deviation of the normal values.
[b]See Ref. 17.
[c]Pre-B plus B cells.
[d]Large lymphocytes and plasma cells.
[e]Fewer than 30 cIg-positive cells per slide investigated.

did not evoke such an attack, except in patient 5, who turned out to have been immunized with HPH previously.

Analysis of the number of T lymphocytes of the peripheral blood showed normal results and the *in vitro* proliferative response to mitogens, antigens, and allogeneic cells did not show abnormalities (data not shown). Analysis of peripheral blood B lymphocytes for expression of surface IgM and IgD showed that patients 14, 15, and 16 did not have immunoglobulin-bearing B lymphocytes in the peripheral blood. This finding is in agreement with the diagnosis of X-linked agammaglobulinemia (XLA) in patients 14 and 15. However, the lack of B cells in common variable hypogammaglobulinemia (patient 16) is unusual. In the patient with an IgM deficiency, normal or even increased percentages of $\mu^+\delta^+$ cells were present. In all other patients tested for the presence of $\mu^-\delta^+$, $\mu^+\delta^+$, and $\mu^+\delta^-$ cells, no abnormalities were found in the blood.

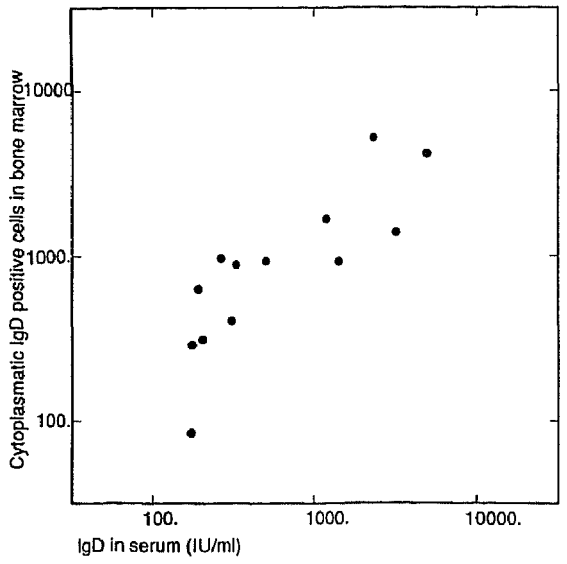

Fig. 3. Correlation between the number of IgD-containing plasma cells in bone marrow and the serum level of IgD.

Bone marrow immunofluorescence studies for plasma cells showed an increase in IgD-containing cells in 14 of 15 patients (Table IVA). The XLA and common variable immunodeficiency (CVID) patients showed decreased numbers of IgM-, IgG-, and IgA-containing plasma cells except for patient 16, who showed an increase in IgM-containing plasma cells, which is in agreement with the presence of IgM in serum (Table II). The patient with an IgM deficiency (patient 17) showed slightly increased numbers of IgM plasma cells, which raises the question of the reason for the deficiency in serum. Several patients showed increased levels of plasma cells of one or more of the three major Ig isotypes. On analysis a linear relationship ($r = 0.82$) between levels of serum IgD and numbers of IgD plasma cells in bone marrow was found (Fig. 3). Analysis of the kappa-to-lambda ratio of cIgD plasma cells showed decreased values in 5 of 13 patients (data not shown). These five patients included the patients with an immunodeficiency syndrome. No attempts were made to determine the kappa-to-lambda ratio in serum IgD.

Combined staining for membrane and cytoplasmic IgM and IgD (see Table IVB) showed that the population of small $cIgM^+$ cells, which include pre-B cells and B lymphocytes, may express sIgM and sIgD simultaneously at a rather high percentage. The XLA patient (No. 14) shows some $sIgM^+$ B lymphocytes in the bone marrow with almost no IgD expression. In patient 15 (XLA) no pre-B cells and B lymphocytes are detectable in the bone marrow, which confirms the lack of B cells in the peripheral blood. The large $cIgM^+$ cells still express surface IgM, but surface IgD expression is less than on the small cIgM cells. The phenomenon of disappearance of surface IgD apparently indicates maturation of B lymphocytes into plasma cells secreting only one Ig isotype, i.e., IgM in this case. A parallel observation is made on large $cIgD^+$ cells which abundantly express sIgD and, to a much lesser extent, sIgM (Table IVB), again indicating maturation of plasma cells committed to produce IgD.

DISCUSSION

In recent years the structure and molecular biology of human IgD have almost been solved (5). In contrast, however, the biological function of this immunoglobulin isotype is far from clear, and almost nothing is known about the meaning of abnormal serum IgD concentrations in patients. Increased serum IgD concentrations have been mentioned, e.g., in pregnancy (21) and in a variety of diseases such as leprosy, tuberculosis (22), parasitic and fungi infection (23), Hodgkin's disease (24), and AIDS (25). Moreover, high serum IgD has been reported in individual patients with various types of immunodeficiency, among which ataxia telangiectasia and Rosen-type dysimmunoglobulinaemia (26) and transient IgD increases have been found after allogeneic bone marrow transplantation (27).

In this study an extremely high serum IgD level was found in the eight patients suffering from the so-called periodic fever hyper-IgD syndrome which was described by van der Meer *et al.* in 1984 (11). This syndrome shows a clinical similarity to familial mediterranean fever (FMF), although in the latter C5a inhibitor deficiency is documented, whereas serum IgD is not increased (11, 28). As argued earlier IgD elevation in periodic fever patients could be either a cause or an effect of an underlying abnormality. van der Meer *et al.* (11) hypothesized that the syndrome consists of an exaggerated and uncontrolled type III hypersensitivity reaction, possibly with involvement of IgD-containing immune complexes. The occurrence of attacks within 1 day after vaccinations with secondary antigens does support this assumption. The striking success of an allergen-free diet in patient 2 would also fit this concept. The present study included the search for serum IgD complexes; surprisingly these were pre-

sent in every serum sample investigated, including those of patients not suffering from periodic fever. Although the composition of the IgD complexes is unknown, their presence in every serum sample indicates that they are not pathognomic for the syndrome of periodic fever. Thus the immune complex nature of this disease is as yet not definitely proven. Selective dysregulation of IgD (and IgA) synthesis in periodic fever by an as yet unexplained mechanism should be envisaged as well and this requires further analysis.

With respect to the serum IgM, IgG, and IgA levels of the patients, the most striking observation concerns the consistent finding of increased serum IgA in the periodic fever patients (see also Ref. 11). A search for IgA-containing complexes was not included in the study. Interestingly in only one of the few patients with periodic fever analyzed for IgA in saliva was an increased level present. Concurrent increases in serum IgD and saliva IgD, although occurring in some patients, were also not the rule (Table III). We are inclined to assume that the serum IgD of the patients reflects predominantly bone marrow-derived IgD (see Fig. 3) and that only some of the patients have increased synthesis of IgD at the level of the salivary gland.

Analysis of *in vivo* IgG antibody production after challenge with tetanus toxoid did not show abnormalities. Recently Litwin and Zehr (29) showed an inverse correlation between high serum IgD levels and lower levels of IgM-type antibodies against phosphoryl choline, tetanus toxoid, and pneumococcal polysaccharide type 3. Our results obtained with the primary antigen HPH showed no correlation between IgM anti-HPH responses and the level of serum IgD. Furthermore, only a few patients showed detectable IgD-class antitetanus or anti-HPH antibodies. We conclude that increases in serum IgD do not imply the generation of antibodies of the IgD class in each individual. In this respect it is interesting to mention the results of Thorbecke and co-workers (30, 31) who showed that injection of myeloma IgD in mice resulted in an enhanced overall antibody response upon antigenic stimulation. This results suggests a role for IgD in the up-regulation of the humoral immune response. However, endogenous increased IgD, as present in our patients, does not lead to an enhanced antibody response upon tetanus or HPH immunization.

Lymphocyte studies did not disclose defects in T-cell function in patients with increased serum IgD. However, the secretion of various cytokines was not investigated. Analysis of the precursor B lymphocytes for IgD plasma cells, i.e., the $\mu^+\delta^+$ and $\mu^-\delta^+$ B cells also did not show abnormalities. In particular, $\mu^-\delta^+$ B cells are not increased in either the peripheral blood or the bone marrow. IgD plasma cells in bone marrow were significantly increased and a bone marrow origin of serum IgD was strongly suggested, as a linear relationship was detectable (Fig. 3). Bone marrow origin of serum IgM, IgG, and IgA has been found earlier (32). The results on double staining for surface IgM and IgD, on the one hand, and cytoplasmic IgM and IgD, on the other, confirm earlier observations that maturation of B lymphocytes into plasma cells is associated with a preponderance of surface Ig of the same isotype as that of the cytoplasm (33). This investigation shows that this phenomenon also holds true for IgD.

The results of this study on a variety of patients with strongly increased serum IgD do not solve the questions concerning the heterogeneity of the associated diseases and the underlying immunological abnormality. However, this inventory raises the question whether there is a certain parallel with the hyper-IgE syndrome where defective regulation of IgE synthesis may be part of the disease entity (34). We are inclined to suggest that regulation of IgD synthesis must be investigated in this patient group including T delta cells and their products (31). With respect to the syndrome of periodic fever, no definite relationship between the clinical signs and the increased serum IgD is apparent. Even the presence of IgD complexes is not contributory since neither the nature and genesis nor the immunopathological consequences are clear. A possible underestimated property of IgD consists of its capacity to bind bacteria in a nonspecific way, i.e., by virtue of the Fc fragment (35). The influence of this phenomenon on the clearance of bacteria in the infected host with increased IgD synthesis, is not clear and deserves investigation.

ACKNOWLEDGMENTS

We are indebted to Mrs. Renee Langlois van den Bergh for performing immunofluorescence on bone marrow cells. Mrs. Linda Gramberg skillfully prepared the manuscript.

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