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IgE Fc receptor positive T and B lymphocytes in patients with the hyper IgE syndrome

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SUMMARY

The percentages of peripheral blood lymphocytes (PBL), bearing Fc receptors for IgE (FcεR) and IgG (FcγR) were determined in four patients with the hyper IgE syndrome by a rosette assay employing IgE and IgG coated fixed ox erythrocytes. The patients had $8 \pm 3\%$ FcεR$^+$ and $13 \pm 8\%$ FcγR$^+$ PBL, compared to $1{\cdot}2 \pm 1\%$ FcεR$^+$ and $17 \pm 4\%$ FcγR$^+$ PBL for control donors. T cells were isolated by rosetting with neuraminidase treated sheep erythrocytes (E_N). Indirect immunofluorescence with Lyt 3 monoclonal antibody (MoAb) to the sheep erythrocyte receptor, followed by rosetting for FcεR and FcγR showed that the patients' T cells contained $< 0{\cdot}1\%$ FcεR$^+$ and $1{\cdot}4 \pm 0{\cdot}2\%$ FcγR$^+$ cells; T cells from the control subjects contained $< 0{\cdot}1\%$ FcεR$^+$ and $11 \pm 4\%$ FcγR$^+$ cells. The non-T (E_N rosette depleted) cells of the patients included $56 \pm 18\%$ sIgM$^+$/sIgD$^+$, $45 \pm 9\%$ FcεR$^+$ and $35 \pm 27\%$ FcγR$^+$ cells. Indirect immunofluorescence with MoAb to IgM, IgD, and NK cells (antibody B73.1) followed by rosetting for FcεR and FcγR, indicated that $92 \pm 2\%$ of the FcεR$^+$ cells and $9 \pm 7\%$ of the FcγR$^+$ cells were B cells (μ^+/δ^+), while $3 \pm 4\%$ of the FcεR$^+$ and $30 \pm 23\%$ of the FcγR$^+$ cells were NK cells (B73·1$^+$). Thus, most of the FcεR$^+$ non-T cells were B cells, and only a small fraction appeared to be NK cells. On the other hand, FcγR$^+$ B cells were outnumbered by FcγR$^+$ NK cells (B73·1$^+$) by three to one. The data indicate that patients with the hyper IgE syndrome have increased numbers of FcγR$^+$ PBL, most of them being B cells, whereas their T cells contain $< 0{\cdot}1\%$ FcεR$^+$ cells.

Keywords hyper IgE syndrome IgE Fc receptors IgG Fc receptors Tε cells Tγ cells

INTRODUCTION

Patients with the hyper IgE syndrome have recurrent staphylococcal abscesses of the skin, lungs, joints and other sites, beginning in infancy; blood and tissue eosinophilia; and extremely elevated serum IgE concentrations (Buckley, Wray & Belmaker, 1971). Although all patients have had a pruritic dermatitis at some time in their lives, the distribution of the lesions is not those of typical atopic dermatitis, and respiratory allergic symptoms are usually absent. The pathogenesis of this disease is unknown. Patients with it show impaired anamnestic IgG antibody responses *in vivo* and poor antibody and cell-mediated responses to neoantigens (Buckley *et al.*, 1971; Buckley & Sampson, 1981). Even though the numbers of B and T cells and T cell subsets are normal (Buckley,

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1983), the patients show depressed *in vitro* responses to soluble antigens (Buckley *et al.*, 1971; Buckley & Sampson, 1981) and to non-HLA identical intrafamilial stimulator cells in mixed leucocyte cultures (Buckley & Sampson, 1981).

Subpopulations of both B (Gonzalez-Molina & Spiegelberg, 1977) and T (Yodoi & Ishizaka, 1979; Thompson *et al.*, 1983) lymphocytes bear the IgE Fc receptor (FcεR). The number of FcεR$^+$ B cells is elevated in patients with atopic dermatitis (Spiegelberg *et al.*, 1979) and in patients with allergic rhinitis during antigen exposure (Spiegelberg & Simon, 1981). The percentage of FcεR$^+$ T cells (Tε cells) is very low ($<0{\cdot}1\%$) in healthy non-atopic humans. However, significant percentages of Tε cells were demonstrated in patients with mild atopic disease (Yodoi & Ishizaka, 1979; Thompson *et al.*, 1983). In contrast, patients with severe atopic dermatitis and highly elevated IgE levels showed $<0{\cdot}1\%$ Tε cells (Thompson *et al.*, 1983). The function of FcεR$^+$ B and T cells is unknown. Studies conducted in rats infested with *Nippostrongylus brasiliensis* suggest that Tε cells have a regulatory role in IgE synthesis (Yodoi & Ishizaka, 1980). Tε cells were reported to release an IgE binding factor which, depending upon its state of glycosylation, either suppressed or potentiated IgE biosynthesis (Yodoi, Hirashima & Ishizaka, 1982). Therefore, we quantified and characterized the FcεR$^+$ peripheral blood lymphocytes (PBL) in four patients with the classic hyper IgE syndrome to determine whether their highly elevated serum IgE levels could result from isotype specific potentiating factors released from elevated numbers of Tε cells.

MATERIALS AND METHODS

Subjects. The four patients with the hyper IgE syndrome had had recurrent severe staphylococcal abscesses of the skin, lungs and other sites from infancy and had markedly elevated serum IgE levels. Clinical and laboratory data on the four patients are listed in Table 1. The absolute lymphocyte numbers of the patients were $3{,}854 \pm 2{,}334/mm^3$ (mean $\pm$ 1 s.d.) as compared to $3{,}080 \pm 910/mm^3$ for the control subjects. Informed consent was obtained from the patients or parents before obtaining blood.

Healthy non-atopic laboratory or clerical workers having less than 25 iu IgE/ml served as control donors. The IgE serum levels were determined either with the Phadebas PRIST reagents (Pharmacia, Inc., Piscataway, New Jersey, USA) or by a previously described radioimmunoassay (Buckley & Fiscus, 1975).

Lymphocytes. PBL were isolated from heparinized venous blood as described (Gonzalez-Molina & Spiegelberg, 1977). Briefly, erythrocytes were sedimented in 1% dextran and the mononuclear cell rich plasma was incubated with colloidal iron; the iron, granulocytes and monocytes were removed with a magnet and the lymphocytes were isolated by Ficoll-Hypaque density centrifugation. The PBL preparations contained $<0{\cdot}2\%$ monocytes as determined by staining for non-specific esterase activity (Koski, Poplack & Blaese, 1976). T cells were enumerated by rosetting with neuraminidase treated sheep erythrocytes (E_N), B cells positive for surface IgM

Table 1. Clinical and laboratory features of four patients with hyper IgE syndrome

Patient	Age	Sex	Age first infection	Dermatitis	Asthma	IgE (iu/ml)	Ly/mm^3
1 (JB)	8	M	1 day	+	0	13,500	3,094
2 (AT)	14	M	Infancy	+	0	6,400	7,310
3 (DS)	24	M	Infancy	0*	0	12,400	2,194
4 (JW)	13	M	6 months	+	+†	36,000	2,820

* Did have earlier in life.
† Very mild.

and IgD were detected by a rosette assay employing ox erythrocytes coated with $F(ab')_2$ anti-IgM or anti-IgD (Spiegelberg & Dainer, 1979).

Purified T cell preparations were isolated by rosetting PBL with E_N for 15 min at 37°C and for 1 h at 4°C, followed by Ficoll-Hypaque density gradient centrifugation as described (Thompson *et al.*, 1979). The cells on the bottom of the gradient were used as T cell enriched fractions after the E_N were lysed with 0·83% NH_4Cl. These preparations contained >95% T cells as judged by staining with monoclonal antibodies (MoAb) Lyt3 (Kamoun *et al.*, 1981) or OKT11 (Berbi *et al*, 1982) which recognize the sheep erythrocyte receptor, and <0·1% monocytes as detected by non-specific esterase staining. Those cells which failed to form rosettes with E_N were collected from the interface of the Ficoll-Hypaque gradient and used as non-T cell (B cell enriched) preparations.

MoAb. T cells were stained with the following commercially available murine MoAb to cell surface antigens: OKT3, OKT4, OKT6, OKT8, OKT11 and OKM1 (Berbi *et al.*, 1982; Reinherz & Schlossman, 1980; Breard *et al.*, 1980) (Ortho Pharmaceuticals, Raritan, New Jersey); Lyt 3 (Kamoun *et al.*, 1981) (clone 9·6, New England Nuclear Corp., Boston, Massachusetts, USA); a mixture of anti-μ chain and anti-δ chain (Bethesda Research Laboratory, Bethesda, Maryland, USA), and B73.1 (Perussia *et al.*, 1983a, 1983b) (K and NK cells, kindly provided by Dr George Trinchieri, Philadelphia, Pennsylvania, USA). The percentages of cells staining with specific MoAb were determined either with a FACS IV (Becton-Dickinson, Mountain View, California, USA) or Ortho Cytofluorograph (System 50-H, No. 2103).

Rosette assays and characterization of FcR^+ cells. Lymphocytes bearing FcεR or IgG Fc receptors (FcγR) were detected by a previously described (Thompson *et al.*, 1983) rosette assay employing fixed ox erythrocytes coated with human IgE or IgG, respectively. Lymphocytes were considered rosette positive if three or more indicator cells were bound. The specificity of the rosettes was determined by inhibition of rosette formation (usually >90%) in the presence of 2 mg/ml soluble IgE or IgG. At least 1,000 T cells were counted to determine the percentage of Tε cells and 300 cells to determine the percentage of Tγ cells.

For characterization of the IgE and IgG rosetting lymphocytes with MoAb, 10^6 lymphocytes were reacted first with MoAb, followed by fluoresceinated goat $F(ab')_2$ anti-mouse Ig fragments (Cappel Laboratories, Cochranville, Pennsylvania) absorbed with normal human IgG. Equal volumes of stained lymphocytes at 10×10^6/ml in RPMI 1640 supplemented with 2·5% fetal bovine serum and 1% indicator red cells were mixed, centrifuged for 3 min at 100*g*, and incubated for 1 h at 4°C. The cells were then gently resuspended in 0·05% toluidine blue to enhance the contrast between lymphocytes and red cells. A Zeiss fluorescence microscope equipped with phase optics was utilized to obtain the percentages of FcR^+ lymphocytes which were also immunofluorescent.

Statistics. The data were analysed statistically with a Student's *t*-test. *P* values >0·05 were not considered significant.

RESULTS

IgE and IgG rosetting lymphocytes in patients with the hyper IgE syndrome

The percentages of IgE and IgG rosetting cells were determined in PBL, T cell, and non-T cell preparations from patients with the hyper IgE syndrome (Table 2). The patients had significantly elevated percentages and absolute numbers of $Fc\varepsilon R^+$ PBL ($8 \pm 3\%$ and $326 \pm 214/mm^3$ *vs* $1{\cdot}2 \pm 1{\cdot}0\%$ and $22 \pm 5/mm^3$) compared to the control donors. In contrast, the percentages of $Fc\gamma R^+$ PBL, E_N^+ cells, and sIg^+ B cells were similar to those of the healthy donors. The isolated T cell preparations contained 0·4 and 0·8% $Fc\varepsilon R^+$ cells in two patients, whereas <0·1% were detected in the other two patients. The contamination with sIg^+ B cells was highest in the two patients having significant percentages of $Fc\varepsilon R^+$ T cells, suggesting that at least some of these cells may have been B cells. The patients had significantly lower percentages of $Fc\gamma R^+$ T cells (Tγ cells) compared to the control donors ($3{\cdot}0 \pm 1{\cdot}3$ *vs* $10{\cdot}5 \pm 4{\cdot}1$). The non-T cells of the patients showed $45 \pm 9\%$ $Fc\varepsilon R^+$ cells, which is significantly higher than the $9 \pm 6\%$ of the control group. The percentages of E_N^+, sIg^+ and $Fc\gamma R^+$ cells in non-T cell preparations from the patients were similar to those of the control group.

Table 2. Cell surface markers of peripheral blood lymphocytes, T cells, and non-T cells from patients with the hyper IgE syndrome

	Percentage rosette forming cells											
	PBL				T(E_N^+)				Non-T (E_N^-)			
Patient	E_N	sIg	FcεR	FcγR	E_N	sIg	FcεR	FcγR	E_N	sIg	FcεR	FcγR
1 (JB)	87	12	10·3	8·5	96	1·2	0·4	2·5	3·0	71	51	65
2 (AT)	86	17	8·2	5·3	96	0·3	<0·1	2·8	2·5	51	54	16
3 (DS)	83	9	3·5	15·5	89	0·4	<0·1	4·8	4·6	32	42	nt
4 (JW)	78	17	11·0	22·2	97	2·0	0·8	1·8	4·3	70	34	54
Mean	84	14	8·3	12·9	95	1·0	0·3	3·0	3·6	56	45	35
s.d.	4	4	3·4	7·5	4	0·8	0·4	1·3	1·0	18	9	27
Control subjects (n=7)												
Mean	77	12	1·2	17·0	97	0·4	<0·1	10·5	5	48	9·1	66
s.d.	11	6	1·0	4·2	3	0·8	—	4·1	2	13	6·3	14

Characterization of IgE and IgG rosetting lymphocytes with MoAb

Isolated T and non-T cells from patients with the hyper IgE syndrome were reacted with a panel of MoAb to lymphocyte surface antigens (Table 3). Except for one patient (No. 3) who had an inverse ratio of $T4^+:T8^+$ cells, the percentages of T cells bearing Lyt 3, T3, T4 and T8 did not differ significantly from those of the control group. The percentages of non-T cells reacting with anti-μ chain + anti-δ chain, B73.1 and OKM1 were also similar for the patients and the control subjects.

A portion of T cells from each patient was stained with the pan-T cell antibody Lyt 3, which is directed to the sheep erythrocyte receptor, and then rosetted for FcεR and FcγR. The IgE and IgG rosetting cells were than examined for positive immunofluorescence. As shown in Table 4, only $14 \pm 4\%$ of the IgE rosetting cells were immunofluorescence positive for the pan-T cell antibody Lyt 3, suggesting that most of the $Fc\varepsilon R^+$ cells in the T cell preparation were non-T cells. An average of 54% of the IgG rosetting cells were immunofluorescence positive for Lyt 3, again indicating the presence of significant proportions of non-T $Fc\gamma R^+$ cells in these preparations. When corrected for the presence of non-T cells, the patients had $<0{\cdot}1\%$ $Fc\varepsilon R^+$ and $1{\cdot}4 \pm 1{\cdot}2\%$ $Fc\gamma R^+$ T cells.

The E_N non-rosetting cells of three patients, stained with anti-μ chain and anti-δ chain, B73.1

Table 3. Percentage T cells and non-T cells reacting with MoAb in patients with the hyper IgE syndrome

	T cells (E_N^+)							Non-T cells (E_N^-)		
Patient	Lyt 3	OKT 3	OKT 4	OKT 8	OKM 1	B73.1	μ^+/δ^+	μ^+/δ^+	B73.1	OKM 1
1 (JB)	98	96	66	26	4	2	2	62	30	nt*
2 (AT)	98	96	56	29	15	3	1	73	6	nt
3 (DS)	96	98	23	45	40	2	0	nt	nt	nt
4 (JW)	92	94	53	39	17	2	1	53	33	31
Mean	96	96	50	35	19	2	1	63	23	—
s.d.	3	2	19	9	15	0·5	1	10	15	
Normal (n=4)										
Mean	98	95	58	34	14	12	1	52	37	38
s.d.	3	4	7	5	8	3	1	9	18	5

* not tested.

Table 4. Percentages of FcR$^+$ cells in T cell preparations from hyper IgE syndrome patients which are also positive for the pan-T cell antibody Lyt 3

Patient	FcεR	FcγR
1 (JB)	10	64
2 (AT)	<10	50
3 (DS)	17	33
4 (JW)	17	67
Mean±s.d.	14±4	54±16

Table 5. Percentages of FcR$^+$ cells in non-T cell preparations from patients with hyper IgE syndrome which are also positive for sIgM and sIgD, B73.1 or OKM 1

	sIgM/sIgD		B73.1		OKM 1	
Patient	FcεR	FcγR	FcεR	FcγR	FcεR	FcγR
1 (JB)	93	17	2	17	nt	nt
2 (AT)	90	5	0	18	nt	nt
4 (JW)	94	6	7	56	8	74
Mean	92	9	3	30	—	—
s.d.	2	7	4	23	—	—

(against K and NK cells) (Perussia *et al*, 1983b) and in one patient with OKM1, were rosetted for FcεR and FcγR. The IgE and IgG rosetting cells were then examined for positive immunofluorescence. As shown in Table 5, 90–94% of the FcεR$^+$ cells reacted with antibodies to μ and δ chains, indicating that they were B cells. Only a small fraction of 2–8% reacted with antibodies B73.1 or OKM1. Approximately 10% of the patients' FcγR$^+$ non-T cells were positive for sIgM + sIgD and 17–56% were B73.1$^+$. In the single case examined, 8% of the FcεR$^+$ and 74% of the FcγR$^+$ non-T cells were OKM1$^+$. Thus, the majority of the patients' FcγR$^+$ non-T cells are not B cells, but rather appear to be K or NK cells as defined by their reaction with B73.1 and OKM1.

Since 92% of the patients' FcεR$^+$ non-T cells were B cells, one can calculate that 74% of their B cells bear FcεR$^+$ (0·92 × 45 of 56). If the same is true for control subjects, then only 17% (0·92 × nine of 48) of their B cells are FcεR$^+$ (see Table 2). Thus, patients with the hyper IgE syndrome have a four- to five-fold increase in the proportion of B cells which bear FcεR.

DISCUSSION

Four patients with the hyper IgE syndrome had significantly more FcεR$^+$ PBL than healthy control donors. The increase was the result of larger percentages and absolute numbers of FcεR$^+$ B cells. Approximately 90% of the IgE rosetting non-T lymphocytes were B cells, as demonstrated by indirect immunofluorescence with anti-μ and anti-δ chain MoAb. From the total number of B cells in these preparations, it was calculated that 74% of the patients' B lymphocytes expressed FcεR as detected by a rosette assay, as compared to 17% for the control donors' B lymphocytes. In contrast, <0·1% of isolated T cells from the patients formed IgE rosettes and reacted with the MoAb Lyt 3 to the sheep erythrocyte receptor. The patients also had few, if any, FcεR$^+$ K or NK cells in either T or non-T cell populations. Only a small percentage of the IgE rosetting cells in T cell depleted lymphocyte preparations showed positive immunofluorescence with B73.1, which recognizes K and

NK cells (Perussia *et al*, 1983a, 1983b). Therefore, the great majority of the increased numbers of FcεR$^+$ lymphocytes in the peripheral blood of patients with the hyper IgE syndrome are B cells. The large number of FcεR$^+$ B cells and lack of FcεR$^+$ T cells in the hyper IgE syndrome patients resembles the findings made previously in patients with severe atopic dermatitis and highly elevated IgE serum levels (Thompson *et al*, 1983; Spiegelberg *et al.*, 1979).

Patients with the hyper IgE syndrome also resemble those with severe topic dermatitis by having low numbers of Tγ cells. Tγ and Tε cells may belong to the same T cell subset since they show a similar pattern of reactivity (Lyt 3$^+$, T3$^-$, T4$^-$ and T8$^+$ or M1$^+$) to a panel of MoAb to T cell surface antigens (Thompson *et al.*, 1983). Since large granular lymphocytes express a similar pattern of cell surface antigens (Phillips & Babcock, 1983; Rumpold *et al.*, 1982), Tγ and Tε cells may belong to its lymphocyte subset. Thus, it appears that patients with the hyper IgE syndrome and atopic dermatitis who have low numbers of Tγ and Tε cells, may have a deficiency of FcR$^+$ large granular lymphocytes.

Patients with the hyper IgE syndrome (Geha *et al.*, 1981) and those with atopic dermatitis (Leung, Rhodes & Geha, 1981) have been reported to have low percentages of OKT8$^+$ T cells. This observation was not confirmed in this or a previous (Buckley, 1983) study of our patients with the hyper IgE syndrome who had either normal or even increased percentages of OKT8$^+$ T cells. Similar findings were observed by Ochs *et al.* (1983). Our findings do not necessarily rule out a functional suppressor T cell defect, however, since the expression of the T8 antigen on lymphocytes does not always parallel the degree of cytotoxic/suppressor function (Thomas *et al.*, 1982).

The function of both T and B cells bearing FcεR is unknown. Tε cells could produce an IgE potentiating factor similar to that reported for rat Tε cells (Yodoi & Ishizaka, 1980) and be responsible for the high IgE serum levels in patients with the hyper IgE syndrome. If so, one would have expected an increase of Tε cells in the patients. Although Tε cells could be increased only in lymphoid organs, this appears unlikely without a concomitant increase in the blood. On the other hand, Tε cells could be isotype specific suppressor cells for IgE synthesis. Tε cells resemble Tγ cells in their cell surface markers, and thus may also be functionally related to Tγ cells. Tγ cells have been shown to suppress pokeweed mitogen driven Ig synthesis *in vitro* (Moretta *et al.*, 1977). A lack of Tε cells would be consistent with the high serum IgE levels in patients with the hyper IgE syndrome. However, functional studies of human Tε cells will be necessary to test this hypothesis.

The function of FcεR on B cells is also controversial. Since 74% of the patients' B cells carried FcεR, it is unlikely that the FcεR is a marker for B cells involved in IgE formation. Even in hyper IgE syndrome patients, IgE represents only a minute fraction of the total immunoglobulin production, and it is extremely unlikely that 74% of the patients' B cells are involved in IgE synthesis. Alternatively, FcεR could play a role in the down regulation of IgE synthesis. Sidman & Unanue (1976) and Ryan *et al.* (1975) showed that the reaction of B cell FcγR with immune complexes inhibits B cell proliferation, suggesting a down regulatory function of B cell FcγR (Moretta *et al*, 1977; Sidman & Unanue, 1976). If the B cell FcεR played a similar down regulatory role, however, one would have expected low rather than high IgE levels in these patients. In contrast, other investigators showed that the addition of Fc fragments (Morgan & Weigle, 1981) or anti-Fc receptor antibodies (Lamars, Heckford & Dickler, 1982) stimulates B cell proliferation. These latter observations would be compatible with the high IgE serum levels and high percentage of FcεR$^+$ B cells in the patients with hyper IgE syndrome. However, functional analyses will be required to determine whether a T cell defect, a B cell defect, or both leads to the overproduction of IgE in patients with the hyper IgE syndrome.

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