

Soluble Fc_εR II levels in normal children and patients with immunodeficiency diseases

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CD23 is expressed on mature B cells and is identical to a low-affinity IgE Fc_ε receptor type II (Fc_εR II). The C terminal portion of CD23 is released to the serum as soluble Fc_εR II (sFc_εR II), which may be involved in regulation of IgE synthesis. We studied sFc_εR II levels in normal children and in patients with immunodeficiencies, including common variable immunodeficiency (CVI), partial DiGeorge syndrome, and immunodeficiency associated with ectodermal dysplasia to examine the relationship of sFc_εR II levels to B cell numbers and other immunoparameters. Serum Fc_εR II levels are higher in younger children (younger than 3 years) and decline gradually with age. In 11 patients with CVI with normal numbers of B cells (>6%), sFc_εR II levels were comparable to that of control subjects. Five patients with CVI with deficiencies of peripheral B cells had levels of sFc_εR II similar to levels of control subjects. In all but one patient with partial DiGeorge syndrome, sFc_εR II levels were not significantly elevated, despite the presence of elevated peripheral B cell numbers. Of six patients with ectodermal dysplasia, four demonstrated increased Fc_εR II levels, a finding not correlated with serum IgE levels or with peripheral eosinophil or B cell numbers. (J ALLERGY CLIN IMMUNOL 1991;87:965-70.)

CD23 Fc_εR II, initially identified as a marker for mature B cells, is known to be expressed on a major subset of peripheral B-lymphocytes as well as on activated T cells, EOSs, macrophages, and platelets.¹⁻⁷ The C-terminal portion of Fc_εR II is released from the cell surface into the serum. Evidence suggests that Fc_εR II is identical to the IgE binding factor(s) reported previously.^{8,9} MAbs against Fc_εR II inhibit in vitro IgE synthesis by normal B cells stimulated with IL-4 and also abolish spontaneous IgE production in vitro by preactivated B cells obtained from atopic patients.¹⁰ IL-4, a key lymphokine in the synthesis of IgE, enhances Fc_εR II expression on human B cells and augments the release of sFc_εR II.^{6,11,12} Thus, it was proposed that the sFc_εR II may play a role in regulation of IgE synthesis, and several investigators have attempted to examine the roles of sFc_εR II and Fc_εR II-bearing lymphocytes in allergic patients. A

Abbreviations used

AR:	Allergic rhinitis
CVI:	Common variable immunodeficiency
ED:	Ectodermal dysplasia
HAD:	Hyperactive airway disease
IL-4:	Interleukin-4
sFc _ε R II:	Soluble Fc _ε receptor type II
MAB:	Mononuclear antibody
Ag:	Antigen
Ab:	Antibody
EOS:	Eosinophil

few studies indicate that the expression of Fc_εR II (CD23) is increased on lymphocytes obtained from atopic patients.¹³⁻¹⁵ Kim et al.¹⁶ reported that serum sFc_εR II levels are elevated in young allergic children (younger than 2 years) in comparison with levels in age-matched, nonallergic children.

In contrast, high IgE levels and increased B cell numbers are often observed in patients with T cell immunodeficiency, such as DiGeorge syndrome, and may be a reflection of dysregulation of IgE synthesis and B cell maturation.¹⁷ However, sFc_εR II levels and their relationship to other immunoparameters have not been well studied in these groups of patients. The present study was designed to examine sFc_εR II levels in normal children and patients with established di-

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Supported by National Institutes of Health Grant AI25062.

Received for publication April 16, 1990.

Revised Dec. 21, 1990.

Accepted for publication Jan. 11, 1991.

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*Dr. Harumi Jyonouchi received a grant from the American Cancer Society, Florida Division.

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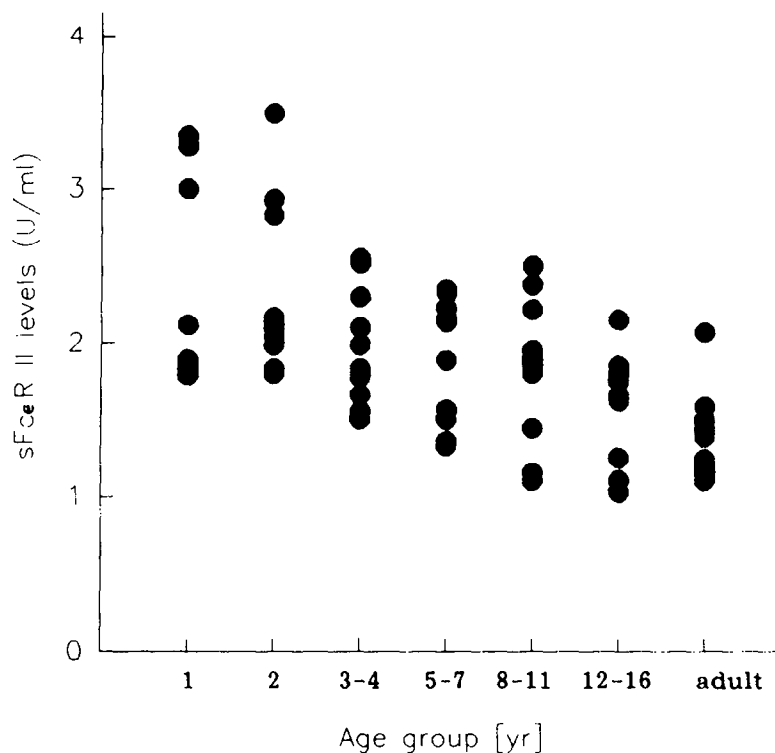


FIG. 1. sFc ϵ R II levels in normal children and adult volunteers. sFc ϵ R II levels were higher in younger children.

agnoses of various immunodeficiency diseases. In our study, sFc ϵ R II levels were found to be poorly correlated to the numbers of peripheral B cells, and even in patients with profound deficiency of B cells, normal levels of sFc ϵ R II levels were present. By contrast, in patients with increased peripheral B cell numbers, sFc ϵ R II levels were not elevated. sFc ϵ R II levels were higher in younger children and declined with age. The Fc ϵ R II levels were also elevated in patients with ED.

MATERIAL AND METHODS

Subjects

Serum Fc ϵ R II levels were quantified in patients with the established diagnosis of immunodeficiency diseases, including patients with CVI who had normal peripheral B cells (CD20⁺ cells, >6%; N = 11; aged 7 to 71 years), patients with CVI with low B cell numbers (CD20⁺ cells, <5%, three of them, CD20⁺ cells <1%; N = 5; aged 3 to 17 years), patients with partial DiGeorge syndrome (N = 5; aged 1½ to 6 years), and patients with ED with immunodeficiencies (N = 6; aged 1½ to 6 years). Samples were also obtained from relatively healthy children of various ages who had been admitted to the hospital for elective surgeries, such as tonsillectomy (N = 75; aged 1 to 16 years). Collected sera were stored at -20°C until the time of assay. As normal control subjects, Fc ϵ R II levels were studied in 16 healthy adult volunteers.

Assay for sFc ϵ R II

Serum sFc ϵ R II levels were studied with a solid-phase ELISA assay. Namely, 96-well, flat-bottom, microtiter plates for ELISA use (Nunc, Thousand Oaks, Calif.) were coated with IgG1 MAbs against Fc ϵ R II (3.5) overnight (10 µg/ml in coating buffer: NaHCO₃, pH 9.6, 0.1 mol/L, and NaN₃, 0.02%).¹³ After wells were washed with rinse buffer (phosphate-buffered saline, pH 7.2, and 0.05% Tween 20), serum samples (50 to 100 µl) or standards were applied to the well and incubated for 2 hours at room temperature. Samples were sometimes diluted with dilution buffer (Tris HCl, 0.05 mol/L, pH 8.1, with MgCl₂, 1 mmol/L; NaCl, 0.15 mol/L; Tween 20, 0.05%; NaN₃, 0.02%; and bovine serum albumin, 1%). Then, after wells were washed vigorously, 50 µl of second Ab (IgM MAbs against Fc ϵ R II [8.30], 2 µg/ml in dilution buffer) and 50 µl of goat antimouse IgM Ab alkaline-phosphatase conjugate (1:500 dilution with dilution buffer, Sigma Chemical Co., St. Louis, Mo.) were added to the well and incubated for 2 hours at room temperature.¹³ The color reaction was elicited by adding substrate solution (p-phenyl phosphate disodium, 1 mg/ml in NaHCO₃, 0.05 mol/L, pH 9.8, and MgCl₂, 10 mmol/L, Sigma Chemical Co.). Color development was detected by spectrophotometer (ELISA reading optical density at 410 and 620 nm). Standards were concentrates of supernatants obtained from a cell line¹⁸ that spontaneously secretes Fc ϵ R II. IgG1 and IgM MAbs against Fc ϵ R II and standards were kindly provided by Drs. H. Kikutani and

T. Kishimoto at Osaka University.¹³ High serum IgE (>1000 IU/ml) appears to interfere with detection of sFc_εR II by ELISA assay, which may be attributed in part to the complexes formed. In patients with high serum IgE levels, serum was diluted to 1:10, and ELISA assay was performed. However, in this study, serum samples with higher serum IgE levels (>600 IU/ml) were not included. When aliquoted serum samples obtained from eight adult volunteers and four patients with CVI were tested repeatedly in this ELISA assay, variations of sFc_εR II levels were <5%. When patients with CVI diseases (N = 6) and patients with partial DiGeorge syndrome (N = 3) were studied for sFc_εR II levels at 6- to 9-month intervals, variations of sFc_εR II levels were <10%.

Cell-surface marker analysis

Percentages of T- and B-lymphocytes and their subpopulations were enumerated in whole blood with MAbs against each cell-surface marker and by flow cytometry (EPICS C and EPICS Elite, Coulter Electronics, Hialeah, Fla.). Unless it is otherwise stated, CD20 Ag was used as pan-B cell marker.

Statistics

For the evaluation of statistical significance, Student's *t* test was used when the *F* test revealed *p* > 0.05, and Welch's test was used when *p* value of *F* test was <0.05.

RESULTS

sFc_εR II levels in control adults and healthy children of various ages

The levels of Fc_εR II were studied in control children of various ages and adult volunteers as described in MATERIALS AND METHODS. The results are presented in Table I and Fig. 1. Younger children were revealed to have higher sFc_εR II levels that are consistent with findings of other studies.¹⁶ The sFc_εR II levels appear to decline with age, as presented in Table I and Fig. 1. The levels of sFc_εR II are statistically higher in age groups of 1 to 2 years compared to adults and age groups 12 to 16 years.

sFc_εR II levels in patients with CVI

In most patients with CVI, normal numbers of B cells are usually present in the peripheral blood. However, in a subset of patients with CVI, peripheral B cells as well as B precursor cells in bone marrow decreased significantly, perhaps reflecting an arrest at early stages of B cell maturation. Since Fc_εR II (CD23 Ag) is expressed on a major subset of mature B cells in the peripheral blood but not among early B precursor cells, we studied sFc_εR II levels in patients with CVI with normal or decreased B cell numbers to examine whether these values are affected by the numbers of peripheral B cells. Eleven patients with CVI

TABLE I. Serum sFc_εR II levels in normal control subjects

Age group (yr)		sFc _ε R II (U/ml)*
1	N = 10	2.43 ± 0.70†
2	N = 11	2.13 ± 0.47‡
3-4	N = 12	1.97 ± 0.35
5-7	N = 10	1.88 ± 0.41
8-11	N = 11	1.89 ± 0.37
12-16	N = 11	1.62 ± 0.35
Adult volunteers	N = 16	1.33 ± 0.24

*Serum Fc_εR II levels were studied by solid-phase ELISA, as described in MATERIAL AND METHODS.

†Compared to adult control subjects and age groups 12 to 16 years, sFc_εR II levels are higher significantly by Welch's test (*p* < 0.001 and *p* < 0.01, respectively).

‡Compared to adult control subjects, sFc_εR II levels were higher statistically (Welch's test *p* < 0.001); compared to an age group 12 to 16 years, sFc_εR II was still significantly high (*p* < 0.01 by Student's *t* test).

(aged 7 to 71 years) with normal numbers of CD20⁺ B cells in the peripheral blood (>6%) and five patients with CVI with decreased CD20⁺ B cell numbers (<5%) were the patients in this study. In the latter group, the deficiency of B cells was also confirmed by analysis with Abs against CD21, CD23, CD19, and surface immunoglobulin. In this group of patients with CVI, CD23⁺ cells in the peripheral blood were all <2%. As illustrated in Fig. 2, sFc_εR II levels were not different in these two groups of patients with CVI, and levels of sFc_εR II were equivalent to those of age-matched control subjects. sFc_εR II levels fell within the normal range in patients with CVI, irrespective of the numbers of peripheral B cells. In patients with CVI with low B cell numbers, peripheral EOS numbers were not significantly elevated. It should be mentioned that even one patient with CVI with very low B cell numbers (<1.0%) and a relatively elevated level of serum IgE (230 IU/ml) had exhibited allergic symptoms, that is, AR and HAD. sFc_εR II levels were not increased in this patient. Furthermore, the correlation between serum IgE levels and Fc_εR II levels were poor in patients with CVI studied (*r* = 0.3454). These results probably indicate that B cells are not a major source of sFc_εR II, at least in these patients.

sFc_εR II levels in partial DiGeorge syndrome

In patients with partial DiGeorge syndrome, increased numbers of peripheral B cells is a common finding. These patients often have elevated serum IgE levels. HAD-like symptoms and autoimmune phenomena are frequent. These abnormalities may be sec-

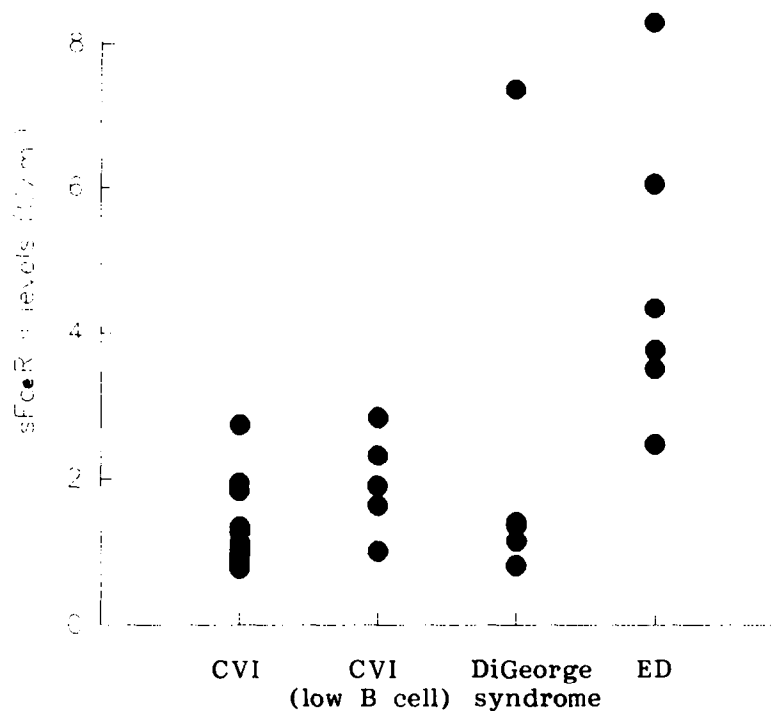


FIG. 2. sFc ϵ R II levels in patients with immunodeficiency diseases. Samples were obtained from patients with CVI with normal B cell numbers, CVI with low B cell numbers, partial DiGeorge syndrome, and ED.

ondary to the T cell dysfunction in these patients.¹⁷ sFc ϵ R II levels were examined in five patients with established diagnoses of partial DiGeorge syndrome who are followed at our immunodeficiency clinic. sFc ϵ R II levels were examined. Peripheral B cell numbers were significantly increased (24% to 54%; $N = 5$) and T cell numbers and serum thymulin levels were decreased in these patients. Two of these patients had autoimmune phenomena represented by autoimmune thrombocytopenic purpura and autoimmune hemolytic anemia. Fc ϵ R II levels were not significantly elevated in patients with partial DiGeorge syndrome except for one patient who also had clinical symptoms of AR and HAD (Fig. 2). In this patient, serum IgE and EOS numbers were not elevated. These results also demonstrate that sFc ϵ R II levels are not influenced by the numbers of B cells in the peripheral blood.

sFc ϵ R II levels in patients with ED

In six patients with ED followed at our immunodeficiency clinic, sFc ϵ R II levels were also studied (aged 1 to 15 years). These patients were found to have mild to moderate immunodeficiency characterized by decreased serum thymulin levels, moderately elevated B cell numbers, deficiency of specific Ab production, and low to low-normal mitogen re-

sponses. The immunodeficiency demonstrated in these patients, however, was quantitatively highly variable in each patient (manuscript in preparation). Four of these patients with ED were observed to have repeated/chronic sinus infections. sFc ϵ R II levels were found to be moderately elevated in four patients compared to age-matched control subjects in this group. Allergic manifestations were revealed in one patient, and peripheral B cell numbers were normal to slightly elevated (Table II). However, no significant correlation was observed between sFc ϵ R II levels and the other immunoparameters, including serum IgE levels, peripheral B cell numbers, and peripheral EOS numbers. CD4/CD8 cell ratios were regularly within the normal range in patients with ED (1.23 to 2.64).

DISCUSSION

The low-affinity Fc ϵ R for IgE is known to be expressed on cells of various lineages, including a major subset of B cells, EOSs, macrophages/monocytes, activated T cells, and platelets.^{4-7, 19} Evidence indicates that soluble Fc ϵ R II, which is released from these cells, is the same as the so-called IgE binding factors.⁸⁻¹⁰ However, the IgE binding factors characterized thus far are of heterogeneous molecular weights, and it may be possible that the size of the Fc ϵ R II varies according to the cellular source from which it derives and even possibly with the function of sFc ϵ R II.^{3, 6, 20-22}

TABLE II. Clinical and laboratory findings in patients with ED

Subject Age/sex (yr)	sFc _ε R II (μ/ml)	CD20 ⁺ cell* (%)	CD3 ⁺ cell (%)	Serum IgE	WBC count/EOS (× 10 ³ /mm ³ %)	Clinical manifestation of allergy
6/F (hypohydrotic ED)	6.05	20	49	114	6.0/0	None
2/F (anhidrotic ED and ectrodactyly)	4.34	40.3	34.2	5.8	10.4/0	None
15/M (anhidrotic ED)	8.35	17	77	519	4.1/9	HAD and AR
2/M (ED with dysautonomia and temp dysregulation)	2.48	39	50	270	8.3/3	None
2/M (ED with congenital cataract)	3.77	35	59	ND	8.8/0	None
2/M (hypohydrotic ED)	2.51	14	77	ND	11.7/0	None

WBC, White blood cell; temp, temperature; ND, not done.

*CD4/CD8 cell ratio ranged 1.23 to 2.63 in these patients, which are all within normal limits. Normal values for CD20⁺ cells and CD3⁺ cells are 7% to 19% and 63% to 85%, respectively.

The functional role of sFc_εR II in IgE synthesis is still somewhat controversial. Delespesse et al.¹² reported that in vitro IgE synthesis by peripheral mononuclear cells after stimulation by IL-4 or the spontaneous production of IgE by B cells obtained from atopic patients is suppressed by MAbs against Fc_εR II. Recent studies of lymphokines revealed that IL-4 exerts an important regulatory action on IgE synthesis in both human and rodent models.²³⁻²⁵ In addition, IL-4 enhances the expression of Fc_εR II on B-lymphocytes.^{6, 11, 12, 26, 27} It is of interest that these actions of IL-4 are suppressed by interferon-γ.^{12, 28} However, IL-4 does not exert such actions on T cells.¹² These results suggest that sFc_εR II may be involved in the regulation of IgE synthesis. Several studies have noted a relative increase of Fc_εR II⁺ B-lymphocytes in atopic patients.¹³⁻¹⁵ Bujanowski-Weber et al.²⁹ reported that the expression of Fc_εR II, as well as the release of sFc_εR II by peripheral mononuclear cells, is enhanced in atopic patients. Kim et al.¹⁶ reported that sFc_εR II levels decline with age and that in early childhood (younger than 2 years), significantly higher levels of Fc_εR II levels were observed in allergic patients. However, the correlation between CD23⁺ (Fc_εR II) B cells and sFc_εR II levels has been poor,¹⁶ and the contribution of sFc_εR II from other cellular sources has not been clarified.

In our study, we also found that in younger children, sFc_εR II levels were higher and that these levels decline with age. It has been established that serum IgE levels increase with age. In patients who have undergone

bone marrow transplantation, a rise in sFc_εR II has been reported to precede the temporary increase of IgE that occurs in the process of immune reconstitution.³⁰ Thus, sFc_εR II may decline in parallel to the significant rise of serum IgE levels, possibly as a reflection of a negative feedback mechanism. Patients with CVI who demonstrated no detectable B cells in the peripheral blood had normal sFc_εR II levels that were comparable to the level observed in control subjects or other groups of patients with CVI who have normal numbers of B cells in the peripheral blood. One patient with Bruton's agammaglobulinemia who lacked B cells entirely was studied, and that patient also demonstrated normal levels of sFc_εR II. In patients with partial DiGeorge syndrome, the defective T cell maturation is often reflected by a dramatic rise in peripheral B cell numbers and a decrease of T cells. Also, these patients develop autoimmune phenomena with high frequency, perhaps secondary to defective T cell regulation.¹⁷ However, in our study, no significant elevation of sFc_εR II was observed in these patients in spite of the fact that peripheral B cell numbers, including CD23⁺ cells, were regularly significantly increased in these patients. One patient with partial DiGeorge syndrome who had AR and HAD did, however, demonstrate elevated sFc_εR II levels. These results suggest that sFc_εR II in the serum is not necessarily a product released by CD23⁺ B-lymphocytes, although B-lymphocytes remain a major population of cells that express Fc_εR II (CD23) in peripheral blood.

sFc_εR II levels were unexpectedly elevated in patients with ED. In these patients, EOS numbers were not impressively elevated, and an sFc_εR II correlation with serum IgE levels was not significant. Recently, Fc_εR II expression by epidermal Langerhans cells was also found to be enhanced by an action of IL-4.³¹ It may be postulated that abnormal skin structure associated with ED may contribute to the elevation of sFc_εR II in these patients. We also observed abnormalities of T cell numbers and functions in patients with ED that are highly variable from patient to patient. Thus, it also appears possible that T cell dysfunctions may have contributed to the elevation of sFc_εR II in patients with ED. Further study of Fc_εR II levels in larger groups of patients with ED will be necessary, since this syndrome is quite heterogeneous.³²

We thank Dr. H. Kikutani and Dr. T. Kishimoto for providing valuable MAbs specific for Fc_εR II.

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