



IgE deficiency. A forgotten disease?

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RESUMEN

Antecedentes: la deficiencia selectiva de IgE se define como la ausencia de IgE sérica (< 5 UI/mL), sin otra anomalía inmunológica. Habitualmente es asintomática, pero puede asociarse con infecciones respiratorias recurrentes, fatiga crónica y complicaciones musculoesqueléticas.

Objetivo: describir la evolución y tratamiento de los pacientes con deficiencia de IgE.

Pacientes y método: estudio retrospectivo en pacientes con deficiencia de IgE e infecciones recurrentes de las vías respiratorias. Se analizó la ficha de identificación, antecedentes de atopía, enfermedades concomitantes, datos clínicos de enfermedades alérgicas, pruebas cutáneas por Prick y respuesta al tratamiento.

Resultados: se registraron 11 pacientes (cinco mujeres y seis hombres) con rango de edad de 16 meses a 10 años. Todos los pacientes tuvieron IgE sérica menor de 5 UI y el resto de las inmunoglobulinas y subclases estuvieron dentro de los parámetros normales al momento del diagnóstico, excepto uno, quien tuvo de forma concomitante deficiencia de IgA. El tratamiento establecido fue desde antibiótico profiláctico hasta gammaglobulina intravenosa mensual, con lo que se observó mejoría clínica.

Discusión: el diagnóstico de deficiencia de IgE se establece en los pacientes con concentraciones séricas iguales o menores de 5 UI, pero el resto de las inmunoglobulinas y subclases dentro de los parámetros normales, asociado con algún cuadro de infecciones recurrentes de las vías respiratorias superiores.

Conclusión: se necesitan más estudios clínicos a largo plazo, para documentar con precisión la deficiencia de IgE.

Palabras clave: deficiencia de IgE, infecciones recurrentes de las vías respiratorias, inmunodeficiencia primaria.

ABSTRACT

Background: Selective IgE deficiency is a profound deficiency (< 5 UI/mL) or absence of serum IgE levels without other immunologic abnormalities. It is usually asymptomatic, but may be associated with recurrent respiratory infections, chronic fatigue, and musculoskeletal complaints.

Objective: To describe the evolution and treatment in patients with selective IgE deficiency.

Patients and method: In selective IgE's deficiency patients identification note, atopy history, concurrent diseases, clinic of allergic diseases, Prick test and prior response to treatment were analyzed.

Results: Eleven patients were included, five women and six men within 16 months to 10 years old. The patients had serum IgE levels < 5 UI with other immunoglobulins and sub-classes in normal levels; except a patient with concomitant IgA and IgE deficiency. The treatment administered was since prophylactic antibiotic to intravenous gammaglobulin.

Discussion: We established the diagnosis of selective IgE deficiency in patient with serum IgE levels < 5 UI/mL associated with recurrent respiratory infections.

Conclusions: We need more clinic studies to document with precision the selective IgE deficiency.

Key words: IgE deficiency, recurrent airway infections, primary immunodeficiency.

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In 1966 Ishizaka et al. demonstrated that the human reaginic antibody was associated with some different kind of immunoglobulin, lately named IgE. Johansson and Bennich described a myeloma protein antigenically identical to IgE, which isolation allowed identifying the chemical features of the immunoglobulin.¹

IgE serum levels in healthy subjects is 100 ng/mL, it is markedly lower than any other immunoglobulin due to its low synthesis index (0.0038 mg/kg/day) besides its catabolic index of 94% of the daily reserve.¹

IgE role in acute hypersensitivity reactions and allergic diseases is well established;² nevertheless, in immunological defense it is unclear: it is known that it does not cross the placenta or fixes the complement, but it is found in external secretions and binds to basophils and mast cells.³ Plasma cells producing IgE are located in mucous tissues of the respiratory and gastrointestinal tract and in the adenoid tissue; thus, the absence of this immunoglobulin results in a poor mucous defense with infection susceptibility.⁴

IgE has a beneficial activity against parasitic infections (*Schistosoma mansoni*) after increasing their destruction by the macrophages; it also has antiviral and antibacterial activity and it might have an important role in some infections control, but in many scenarios, its serum concentration is too low to act as a neutralizing antibody, overall when there is a great antigenic burden, as this is the case of infections. IgE has alternate function in the immune defense, including acting as a cofactor to modify the microenvironment, due to its ability to release mast cell mediators which alter vascular permeability and to release the cell and humoral components in the site of infection, helping in an indirect way to clearance or elimination of pathogen agents.^{4,5}

The report by Ammann, Cain, Ishizaka Hong and Good in 1969 describes the interesting function of IgE in host defense. In this study, a greater sinopulmonary infection susceptibility was observed in patients with ataxia and telangiectasia associated with a combined IgA and IgE deficiency, but not in those with ataxia and telangiectasia with only IgA deficiency.³ In 1975 Buckley et al. observed in 165 patients with primary immunodeficiency, that the IgE concentration was significantly diminished, in comparison with the control group (healthy volunteers).^{3,4,6}

Selective IgE deficiency is described as a concentration below 5 UI/mL or the definite absence of serum IgE without another immunological abnormality. Those patients do not manifest signs,^{4,6,7} but it can be associated with recurrent respiratory infections, chronic fatigue and musculoskeletal complications.^{6,8}

Schoettler et al. reported a family with the IgE deficiency association with chronic sinopulmonary infections. The analysis of three generations suggested

an autosomal dominant inheritance with a variable penetration.^{4,6}

In the Smith and Krishnaswamy research (1997) IgE concentrations were determined in 420 adult patients from the Allergy and Immunology Department; 44 patients had concentrations below 2.5 UI/mL; 57% of those had reduced concentrations of other immunoglobulins^{9,10} and 43% showed isolated IgE deficiency. They found that patients with IgE deficiency frequently manifested arthralgia and myalgia ($p<0.0001$), chronic fatigue ($p<0.0001$) and symptoms suggestive of respiratory tract infection ($p=0.0119$), in comparison with patients with normal or elevated IgE, besides a greater prevalence of autoimmune diseases ($p<0.0001$).^{6,9}

IgE replacement in these patients is not feasible due to its low plasma level and its short half life. The treatment for the underlying disease is warranted.⁶

Replacement therapy with intravenous gammaglobulin is indicated for those cases with recurrent infections and IgG subclasses more than two standard deviations below normal mean for age.¹¹

PATIENTS AND METHODS

Patients with IgE deficiency and recurrent respiratory tract infections diagnosis were selected from the files of the Allergy and Immunology Department of the Regional Hospital ISSSTE' Clinic Lic. Adolfo Lopez Mateos. The study period went from May to December 2007.

There were found 13 patients with similar or lower concentrations than 5 UI/mL of IgE, but 2 cases were excluded due to incomplete data on file.

From the 11 patients enrolled in the trial, an identification file was obtained from the medical history and they were searched for atopy, infections (pneumonia), sinusitis and comorbidities (gastroesophageal reflux diagnosed by clinic and x-ray tests) and onset of repetitive infections.

Patients underwent interrogation to search for allergic rhinitis and asthma (cutaneous Prick testing; specific immunotherapy was initiated in those with positive results).

On all patients the serum concentration and nasal mucus eosinophil concentrations were determined; coproparasitoscopic tests and IgA, IgG, and IgM con-

centrations were performed. In only seven instances the IgG subclasses were determined.

RESULTS

Distribution by sex was 5 women and 6 men, with an age range of 16 to 120 months (10 years). Symptoms onset was from 2 to 12 months of age.

Seven patients had atopy history, from these, 5 fulfilled allergic rhinitis and asthma criteria by positive cutaneous tests.

Patients 9 and 10 had atopy history without clinical signs of allergic disease; their cutaneous tests were negative.

Eight cases had a diagnosis of gastroesophageal reflux, in those patients a specific treatment was initiated.

Peripheral eosinophils concentration varied between 80 and 700/mm³; no correlation with another allergic disease was found (table 1).

Only patient 8 showed concurrent IgA deficiency. The rest of serum immunoglobulin concentrations were within normal range for age (table 2).

DISCUSSION

All 11 patients were children with recurrent upper respiratory tract infections (pharyngitis, pharyngoamygdalitis, and sinusitis). Recurrent infections were defined as infections occurring every 15 days or once a month.

In all cases IgE serum concentrations determined were below 5 UI, but the rest of the immunoglobulins and subclasses were within normal range at the time of the diagnosis, except for patient 8 (table 2).

One of the issues that stand out was the following: why did patients 1, 2, 4, 5, and 10 have positive cutaneous tests, even with low or barely inexistent IgE?; the hypothesis which could explain this event is that maybe there is more IgE bound to mast cells, with the ability

Table 1. Patients clinical history

Patient	Age (years)	Sex	Illness onset (months)	Atopy	GERD	Pneumonia	Sinusitis	Allergic asthma	Allergic rhinitis	Serum eosinophils
1	10	Female	10	(+)	(+)	1	3	(+)	(+)	100
2	4	Female	2	(+)	(+)	0	1	(-)	(+)	100
3	8	Female	2	(-)	(-)	0	2	(-)	(-)	100
4	1 year 11 months	Male	2	(+)	(+)	0	0	(+)	(+)	300
5	2 years 5 months	Male	12	(+)	(+)	0	0	(+)	(+)	100
6	4	Male	7	(-)	(+)	0	2	(-)	(-)	700
7	1 year 4 months	Male	7	(-)	(-)	0	0	(-)	(-)	100
8	2 years 6 months	Male	12	(+)	(+)	3	1	(-)	(-)	80
9	3 years 1 month	Female	3	(+)	(+)	0	0	(-)	(-)	200
10	2 years	Female	3	(+)	(+)	0	2	(+)	(+)	100
11	4 years 3 months	Male	12	(-)	(-)	0	2	(-)	(+)	200

GERD: gastroesophageal reflux disease.

Table 2. Tests and immunoglobulin determinations

<i>Patient</i>	<i>Copro- parasitosc- pic test</i>	<i>IgG (mg/dL)</i>	<i>IgM (mg/ dL)</i>	<i>IgA (mg/ dL)</i>	<i>IgE (UI/ mL)</i>	<i>IgG subclasses</i>	<i>Cutaneous tests</i>	<i>Treatment</i>	<i>Evolution</i>
1	(-)	1,502	317	150	< 1.0	IgG1: 1,110 (380-1,420), IgG2: 705 (73-455), IgG3: 67 (16-194), IgG4: 26 (1-153)	Dust ++, DPT ++, DF ++	Intravenous gammaglo- bulin, specific immunotherapy and anti-reflux treatment	Favorable
2	(-)	1,360	81.2	101	5	IgG1: 1,170 (290-1,065), IgG2: 672 (28-315), IgG3: 65 (4-71), IgG4: 16 (1-90)	Cat + Ash tree++	Intravenous gammaglobulin and anti-reflux treatment	Favorable
3	(-)	901	212	86	< 3.9	Non-performed	Negative	Intravenous gammaglobulin	Favorable
4	(-)	902	59	45.9	4.6	IgG1: 830 (290-1,065), IgG2: 73 (28-315), IgG3: 33 (4-71) IgG4: 9 (1-90)	DF +++ House dust ++	Oral immuno- therapy, prophylactic antibiotics and anti-reflux treatment	Favorable
5	(-)	1,050	83.6	71.7	4.6	IgG1: 639 (290-1,065), IgG2: 121 (28-315), IgG3: 38 (4-71), IgG4: 5 (1-90)	Acarus ++ House dust ++	Subcutaneous immunothera- py, prophylactic antibiotics and anti-reflux treat- ment	Favorable
6	(-)	951	113	65.5	3.9	IgG1: 696 (330-1,065), IgG2: 384 (57-345), IgG3: 32 (8-126), IgG4: 94 (2-116)	Negative	Prophylactic antibiotics and anti-reflux treat- ment	Favorable
7	(-)	680	42	37.1	4.6	IgG1: 634 (170-950), IgG2: 61 (22-240), IgG3: 57 (13-69), IgG4: 8 (1-120)	Negative	Prophylactic antibiotics	Favorable
8	(-)	1,140	92	50	4.6	Non-performed	Negative	Intravenous gammaglobulin and anti-reflux treatment	Favorable
9	(-)	1,060	131	23.5	5	Non-performed	Negative	Prophylactic antibiotics and anti-reflux treat- ment	Favorable
10	(-)	966	149	110	5	IgG1: IgG2: 81.8 (52-280), IgG3: 55.1 (14-120), IgG4: 2.6 (3-106)	DF ++	Subcutaneous immunothera- py, prophylactic antibiotics and anti-reflux treat- ment	Favorable
11	(-)	1,070	79.7	171	5	Non-performed	Negative	Prophylactic antibiotic	Favorable

to develop a positive reaction in cutaneous tests; while free IgE is quantified in serum determinations and it is therefore detected in concentration well below normal range.

The prescribed treatment for each patient depended on the frequency and severity of the infections: from prophylactic antibiotics in monotherapy to intravenous gammaglobulin (400 mg/kg/month), which showed clinical improvement, with longer timeframe of respiratory infections and reduction of severity.

It has been reported that intravenous gammaglobulin contains no IgE; then, the question is why do patients with IgE deficiency had a favorable reaction with this treatment?, other situations had to be discarded, those which favored repetitive infections in study patients; a suspected diagnosis which may be the cause of the favorable response to treatment may be caused by some deficiency related with the response to polysaccharides (an alteration distinguished by recurrent bacterial respiratory tract infections, with a subnormal or absent response to most of polysaccharide antigens, normal concentrations of IgG and subclasses with intact response to proteic antigens). Common respiratory infections are chronic otitis, sinusitis and bronchitis; occasionally there may be more severe infections like mastoiditis, meningitis or pneumonia, which may result in bronchiectasis. The most frequent cause is related with microorganisms with polysaccharide capsule (*pneumococcus*, *H. influenza*, *meningococcus* and group B *streptococcus*).

Allergic diseases (asthma or rhinitis) occur in more than 50% of patients with failure of antibody response to polysaccharides; most of them have a history of assisted ventilation, adenoidectomy, amygdalotomy and history of multiple antibiotics administration.¹²⁻¹⁶

In table 3 there are shown the serum determinations of IgE in different times. An increase in IgE levels was seen as the patients evolved, which allowed us to establish, as a hypothesis, that while the patient reached an older age, in a parallel way, exposing to sensitization of more and new allergens increased the production of IgE and other immunoglobulins.

More prospective studies with a larger number of patients are required to prove persistence of diminished IgE. With this the possibility of classifying IgE deficiency

Table 3. Serum determination of IgE in different times

No. of patient	IgE determination
1	1, <18, 24, 29, 24.7
2	1.67, 5, 7, 14, 23
3	<1.6, <1.6, 3.9, 5, 5, 7.2
4	4.6, 4.6, 5, 5, 8.
5	4.6, 10, 8, 10, 17
6	<1.6, 5.7, <1.7, 6, 8, 24
7	4.6, 4.6, 3.9, 9.5, 13.3
8	3.9, 9.5, 13.3, 15, 16.5
9	<1.6, <1.6, 3.4, 4, 5
10	2, 5, 7.5, 9.0, 9.0, 11.0
11	3.0, 2.8, 5.5, 10.3, 13.2

cy as transient or persistent will be open, as long as the exclusion of other diseases.

CONCLUSIONS

Recurrent respiratory tract infections are a frequent cause of consultation. Besides discarding allergic causes and the exacerbating phenomenon of infections, it is important to discard any primary or secondary immunodeficiency.

The assessed patients did not show any disturbance at physical examination or growth failure; nevertheless, their clinical history showed repetitive infections. According to the former, we consider that in pediatric patients with normal physical examination and history of recurrent infections, IgE deficiency must be suspected as a diagnosis option, as long as other alterations like failure of antibody response to polysaccharide.

During each patient evaluation, diagnosis tests (IgG, IgM, and IgA, and if available, IgG subclasses) can be found within normal parameters, except for IgE which can have values lower than 5 UI/mL, for which deficiency of IgE would be considered.

Because its diagnosis is variable, long-term follow up is suggested; some children, after the age of three, will have an appropriate response to polysaccharides and will balance their IgE levels; nevertheless, others will have a persistent IgG subclass deficiency or common variable immunodeficiency.¹³

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