Relationship between immunoglobulin-E deficiency and autoimmune disease: the paradigm of primary biliary cholangitis

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Immunoglobulin E (IgE) deficiency (usually defined as a serum concentration <2.5 kU/L or <2 kU/L) [1,2] has been gaining attention in recent years [1-5]. Low serum IgE does not always indicate a clinical disorder and is not considered a primary immunodeficiency *per se* [2] but can be associated with susceptibility to certain infections, nonallergic airway disease, recurrent infection, cardiovascular disease, malignancy, and autoimmunity [1-5]. Primary biliary cholangitis (PBC; formerly known as primary biliary cirrhosis) is an autoimmune disease characterized by cell-mediated (sometimes granulomatous) destruction of intrahepatic bile ducts, portal inflammation and progressive fibrosis [6]. The disease is more common in women and can be associated with a variety of immune disorders. The most well-known humoral disorder in PBC is serum IgM elevation [7]. To our knowledge, only one study has investigated serum IgE concentrations in patients with PBC. In 1989, Minuk et al. [8] showed that 14/22 (64%) patients with PBC had low (<10 kU/L) serum IgE levels. Moreover, 10 patients (45%) had IgE levels below the level of detection of an immunoenzymatic method [8]. The present study aimed to investigate the prevalence of serum IgE deficiency and its clinical associations in patients with PBC, compared with a general adult population. The study was approved by the regional ethics committee.

The study included 50 patients with PBC who were treated in a liver disease unit of a university hospital. All patients fulfilled the criteria for PBC, including at least two of the following: 1) increased serum alkaline phosphatase (ALP) levels; 2) presence of antimitochondrial antibodies; and 3) compatible liver biopsy with bile duct lesions [9]. Patients with overlap criteria with autoimmune hepatitis [9] were excluded. The patients' clinical characteristics are presented in Table 1. The control population was made up of 1516 adult individuals from a municipality whose reference hospital is the same as that of the PBC patients in the study. The selection of these subjects was done at random and was not influenced by atopy or other diseases. The study characteristics and immunoglobulin concentrations for this population have been reported elsewhere [10-12]. Serum IgE concentrations were significantly lower in the patients with PBC than in the control population (Table 1). Conversely, serum IgG and, particularly, IgM concentrations were higher in the patients with PBC (Table 1). Serum IgE concentrations were not correlated with liver damage markers (serum bilirubin, ALP, and GGT) in the patients with PBC (P>0.5 in every case). In contrast, serum IgM concentrations were positively correlated with serum ALP and GGT levels (Rho 0.452 [P<0.001] and 0.409 [P=0.003], respectively; Spearman's rank test).

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Serum IgE deficiency (<2.5 kU/L [1,2]) was present in a third of patients with PBC (Table 1) and in 8% (95% confidence interval, 6.6%-9.4%) of the individuals from the general adult population (P<0.001, chi-squared test). Deficiency of IgE was selective (i.e., with normal [>700 mg/dL] IgG and normal [>70 mg/dL] IgA concentrations) [4] in all 16 cases of PBC and in 111/121 (91.7%) of cases from the general adult population (six individuals with IgE deficiency showed mild IgG deficiency [range, 548-682 mg/dL]; two individuals showed undetectable IgA concentrations, and two showed mild IgA deficiency [47-61 mg/dL]). No more inborn errors of immunity were present in the sample. In the general adult population, IgE deficiency was associated with lower IgG and IgA concentrations, older age, female sex, lower rate of respiratory allergy, and a higher rate of autoimmune disease, particularly, autoimmune thyroid disease (hypothyroidism in most cases) (Suppl. Table 1). Autoimmune thyroid disease was present in 10/121 (8.3%) of the participants with IgE deficiency versus 42/1345 (3.0%) of the participants with higher IgE concentrations (P=0.033, chi-squared test). The association between IgE and autoimmune thyroid disease was still present after adjusting for age and sex (data not shown). Moreover, there was a trend toward a lower prevalence of autoimmune thyroid disease with increasing IgE concentration (P<0.001) (Suppl. Table 1). The prevalence of autoimmune thyroid disease was lowest (2/346, 0.6%) among the participants with high (>100 kU/L) IgE concentrations, who in turn showed the highest prevalence of allergic respiratory disease (117/346, 33.9%). Likewise, the patients with PBC, who are characterized by low serum IgE concentrations, showed a low rate of respiratory allergy and a very high rate of autoimmune thyroid disease (Table 1). Neither the patients with PBC nor the participants from the general adult population with IgE deficiency reported a history of recurrent bacterial or helminth infections (Suppl. Table 1).

These results suggest that liver disease *per se* does not seem to be a cause of increased serum IgE concentrations. Certain causes of cirrhosis such as alcohol abuse are associated with increased IgE levels [13] whereas others are associated with low IgE levels, such as PBC, in which nearly two-thirds of patients showed concentrations <10 kU/L, in agreement with previous reports [8]. The results are also consistent with an association between IgE deficiency and autoimmune disease, particularly thyroid disease [2,3,5]. The patients with low IgE concentrations, such as those with PBC, showed a high prevalence of autoimmune thyroid disease, which was also associated with IgE deficiency among the individuals from the general adult population. The prevalence of IgE deficiency in the general population was similar to that reported previously in specific clinical settings [3]; however, those affected were mostly

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asymptomatic. It is possible that selection bias towards symptomatic cases occurs in studies of IgE deficiency in specific clinical units but not in studies of participants who are randomly sampled from the general population. As expected, low IgE concentrations (as observed in the patients with PBC and the individuals from the general adult population) were negatively associated with respiratory allergy. Taken together, the results are consistent with a bias toward type-1 rather than type-2 cytokine responses in patients with PBC, as has been shown in peripheral blood mononuclear cells [14]. The hypothesis is further supported by the finding of low serum IgE concentrations in patients with sarcoidosis, a granulomatous disease with similarities and occasional overlapping with PBC [15]. Autoimmune diseases other than from thyroid disease were rare in the general population so as to investigate their relationship with IgE deficiency (Suppl. Table 1). Further studies are needed to investigate whether similar IgE findings are present in additional cell-mediated immune diseases.

Key words: IgE. IgE-deficiency. Primary biliary cholangitis. Autoimmune-disease.

Palabras clave: IgE. Deficiencia de IgE. Colangitis biliar primaria. Enfermedad autoinmune.

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Table 1. Demographic, clinical, and immunological characteristics of patients with primary biliary cholangitis and individuals from the general adult population.

	Primary biliary cholangitis (n=50)	**General adult population** (n=1516)	**P-value**
Age (years)	58 (48-66)	52 (39-67)	0.086
Sex (female)	42 (84.0)	838 (55.3)	<0.001
Autoimmune thyroid disease*	11 (22.0)	52 (3.4)	<0.001
Respiratory allergy	2 (4.0)	197 (12.9)	0.096
Serum IgG (mg/dL)	1400 (1150-1550)	1080 (931-1240)	<0.001
Serum IgA (mg/dL)	224 (156-320)	217 (162-285)	0.863
Serum IgM (mg/dL)	304 (210-495)	96 (66-137)	<0.001
Serum IgE (kU/L)	6 (1-14)	28 (8-87)	<0.001
Serum IgE categories			
>100 kU/L	2 (4.0)	346 (22.8)	<0.001
10-100 kU/L	17 (34.0)	765 (50.5)	
2.5-9.9 kU/L	15 (30.0)	284 (18.7)	
<2.5 kU/L	16 (32.0)	121 (8.0)	

Data are presented as medians and interquartile ranges (within parentheses) or absolute numbers and percentages (within parentheses). *Hypothyroidism in all cases, except Graves' disease in one case of primary biliary cholangitis and 4 cases among the individuals from the general population. Serum IgE was measured by chemiluminometric immunoassay (ADVIA Centaur, Siemens Healthcare Diagnostics). The 2 patients with PBC and respiratory allergy had IgE concentrations of 39 kU/L and 162 kU/L. Serum IgG, IgA and IgM were measured by immunonephelometry (BNII™ System, Siemens Healthcare Diagnostics). P-values were obtained after comparison between patients with primary biliary cholangitis and individuals from the general adult population by means of the Mann-Whitney test (for numerical variables) or the chi-squared test with Yates correction (for proportions, including the distribution of IgE in categories), where appropriate.

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