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], although it may be associated with susceptibility to 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 elevated serum IgM concentrations [7].

To our knowledge, only 1 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 serum IgE concentrations (<10 kU/L). Moreover, 10 patients (45%) had concentrations below the level of detection based on 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 the general adult population. The study was approved by the regional ethics committee.

The study included 50 patients with PBC who were treated in the liver disease unit of a university hospital. All patients fulfilled the criteria for PBC, including at least 2 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 in whom the criteria overlapped with those of autoimmune hepatitis [9] were excluded. The patients’ clinical characteristics are presented in the Table. The control population comprised 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 patients was 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). Conversely, serum IgG and, particularly, IgM concentrations were higher in the patients with PBC (Table). Serum IgE concentrations were not correlated with markers of liver damage (serum bilirubin, ALP, and γ-glutamyl transferase [GGT]) in patients with PBC (P>.5 in each case). In contrast, serum IgM concentrations were positively correlated with serum ALP and GGT levels (p=0.452 [P<.001] and 0.409 [P=.003], respectively; Spearman rank correlation test).

Serum IgE deficiency (<2.5 kU/L [1,2]) was present in a third of patients with PBC (Table) and in 8% (95%CI, 6.6%-9.4%) of the individuals from the general adult population (P<.001, χ2 test). IgE deficiency was selective (ie, with normal IgG [>700 mg/dL] and normal IgA [>70 mg/dL] concentrations) [4] in all 16 cases of PBC and in 111/121 (91.7%) of cases from the general adult population (6 individuals with IgE deficiency had mild IgG deficiency [range, 548-682 mg/dL], 2 individuals had undetectable IgA concentrations, and 2 had mild IgA deficiency [47-61 mg/dL]). Noborn 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 (hyperthyroidism in most cases) (Supplementary table 1). Autoimmune thyroid disease was present in 10/121 (8.3%) of the participants with IgE deficiency compared with 42/1345 (3.0%) of the participants with higher IgE concentrations (P=.033, χ2 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 concentrations (P<.001) (Supplementary table 1). The prevalence of autoimmune thyroid disease was lowest (2/346, 0.6%) among the participants with high IgE concentrations (>100 kU/L), who in turn had the highest prevalence of allergic respiratory disease (117/346, 33.9%). Likewise, patients with PBC, who were characterized by low serum IgE concentrations, had a low rate of respiratory allergy and a very high rate of autoimmune thyroid disease (Table). 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 (Supplementary 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 excess alcohol intake, are associated with increased IgE levels [13], whereas others are associated with low IgE concentrations, for example, PBC, in which nearly two-thirds of patients had <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, had a high prevalence of autoimmune thyroid disease, which was also associated with IgE deficiency among 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 asymptomatic. Selection bias toward symptomatic cases may be found in studies on IgE deficiency in specific clinical units but not in studies on 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, these results are consistent with a bias toward type 1 rather than type 2 cytokine responses in patients with PBC, as 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 that is similar to and occasionally overlaps with PBC [15]. Autoimmune diseases other than thyroid disease were rare in the general population, thus making it difficult to investigate their relationship with IgE deficiency (Supplementary Table 1). Further studies are needed to investigate whether similar IgE findings are present in additional cell-mediated immune diseases.

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**References**


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