

Chronic Sinopulmonary Inflammatory Diseases in Adults with Undetectable Serum IgE in Inner-City Chicago: A Preliminary Observation

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Abstract

Background The association between undetectable serum total IgE level and chronic upper and lower respiratory tract inflammatory diseases is uncertain. We sought to determine whether chronic sinopulmonary inflammatory diseases are present in adult patients with undetectable serum total IgE who reside in inner-city Chicago, IL, USA. **Methods** Medical records of patients aged ≥ 18 years with reported serum total IgE levels < 2 and $\geq 2,000$ kU/L who were diagnosed with rhinitis, chronic rhinosinusitis, asthma, and COPD at the University of Illinois Medical Center and Jesse Brown VA Medical Center, Chicago, IL, between 2005 and 2009 were reviewed.

Results Seventeen patients with serum total IgE < 2 kU/L and 17 patients with serum total IgE $\geq 2,000$ kU/L, were identified. Ten of 17 patients (59%) with serum total IgE < 2 kU/L were diagnosed with chronic sinopulmonary inflammatory diseases, three with chronic rhinosinusitis, four with asthma, one with asthma/COPD, and two with COPD. Twelve of 17 patients (71%) with serum total IgE $\geq 2,000$ kU/L were diagnosed with chronic sinopulmonary inflammatory diseases, three with allergic rhinitis, four with asthma, four with asthma/COPD, and one with COPD. None of the patients reported recurrent sinopulmonary infections. The difference in the number of patients with chronic sinopulmonary inflammatory diseases between both groups was not statistically significant ($p = 0.48$).

Conclusions Chronic rhinosinusitis and asthma are present in adult patients with undetectable serum total IgE who reside in inner-city Chicago. Whether this represents a biomarker of distinct chronic rhinosinusitis and asthma phenotypes in this population remains to be determined.

Keywords Asthma · COPD · Rhinosinusitis · Allergy · ImmunoCap Total IgE · Immunoglobulins

Introduction

It is well established that high serum total IgE level is associated with chronic upper and lower respiratory tract allergic diseases, most notably allergic rhinitis and asthma [1–4]. Whether serum total IgE level below the detection limit (2 kU/L) of a commonly used commercial total IgE assay is associated with chronic sinopulmonary inflammatory diseases is controversial.

While several studies have reported an increased prevalence of chronic sinopulmonary inflammatory diseases in patients with selective IgE deficiency, including rhinosinusitis, chronic bronchitis, and asthma, other investigators were unable to reproduce this observation [5–9]. For example, Smith et al. [5] reported that 32 of 44 adult patients (73%) with a serum total IgE level ≤ 2.5 IU/mL in rural eastern Tennessee had physician-diagnosed asthma compared to 20% in those with a normal or an elevated serum total IgE level. The prevalence of chronic rhinosinusitis was not reported. By contrast, Levin et al. [6] detected extremely low serum total IgE levels (≤ 2.1 IU/mL) in 20 pregnant women residing in southeastern Michigan, with no significant difference in the prevalence of physician-diagnosed asthma in comparison to pregnant women with serum total IgE ≥ 2.1 IU/mL. However, the

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former group had significantly lower prevalence of physician-diagnosed rhinosinusitis.

To the best of our knowledge, no studies have examined the presence of chronic sinopulmonary inflammatory diseases in patients with undetectable serum total IgE (<2 kU/L) residing in inner-city Chicago, IL, USA, where they are exposed continually to both indoor and outdoor air pollution as well as aeroallergens [10, 11]. To this end, no physician-diagnosed asthma was reported among subjects with very low serum total IgE levels residing in Tucson, AZ, an urban community located in an arid region of the southwestern US [12].

Given the relatively high prevalence of chronic sinopulmonary inflammatory diseases in inner-city Chicago [10, 11], the purpose of this study was to determine whether chronic sinopulmonary inflammatory diseases are present in adult patients with undetectable serum total IgE in comparison to those with exceedingly high ($\geq 2,000$ kU/L) serum total IgE levels residing in inner-city Chicago.

Methods

The medical records of patients aged 18 years and older with serum total IgE levels <2 and $\geq 2,000$ kU/L (ImmunoCap Total IgE, Phadia AB, Uppsala, Sweden; detection range = 2–5,000 kU/L) seen at the outpatient clinics of the University of Illinois Medical Center and Jesse Brown VA Medical Center in Chicago between 2005 and 2009 were reviewed. The total IgE assay used in this study is calibrated against the WHO human IgE reference serum 75/502.

Only patients with an established diagnosis of allergic rhinitis, chronic rhinosinusitis, asthma, and COPD based on clinical practice guidelines were included in the study [13–16]. None of the patients thus identified was diagnosed with immunodeficiency disorders, other hypogammaglobulinemias, allergic bronchopulmonary aspergillosis, hyperimmunoglobulin E (Job's) syndrome, ataxia-telangiectasia, or alcoholism. An allergen-specific IgE antibody test was not performed in any of the patients enrolled in this retrospective study (see below).

The study was approved by the Institutional Review Board of University of Illinois and Jesse Brown VA Medical Center.

Data and Statistical Analyses

The presence of chronic sinopulmonary inflammatory diseases was evaluated as a binary variable (present or absent). Bivariable analyses were performed using two-tailed Fisher's exact test for a 2×2 contingency table and $p < 0.05$ was considered statistically significant.

Results

Seventeen patients (6 males and 11 females) with serum total IgE <2 kU/L and 17 patients (15 males and 2 females) with serum total IgE $\geq 2,000$ kU/L were identified. Age ranged from 21 to 90 and 47 to 92 years, respectively. Four patients with serum total IgE <2 kU/L were current smokers, four were ex-smokers, and nine were life-long nonsmokers. Seven patients with serum total IgE $\geq 2,000$ kU/L were current smokers, seven were ex-smokers, and three were life-long nonsmokers ($p = 0.07$ between groups of patients with present and past history of smoking).

Ten of 17 patients (59%) with serum total IgE <2 kU/L were diagnosed with chronic sinopulmonary inflammatory diseases: three with chronic rhinosinusitis (one ex-smoker and two life-long nonsmokers), four with asthma (life-long nonsmokers), one with asthma/COPD (ex-smoker), and two with COPD (current smokers). Twelve of 17 patients (71%) with serum total IgE $\geq 2,000$ kU/L were diagnosed with chronic sinopulmonary inflammatory diseases: three with allergic rhinitis (two current smokers, one ex-smoker), four with asthma (three life-long nonsmokers, one ex-smoker), four with asthma/COPD (two ex-smokers; two current smokers), and one with COPD (current smoker).

No distinctive clinical features distinguished patients with chronic sinopulmonary inflammatory diseases and undetectable serum total IgE from those with serum total IgE $\geq 2,000$ kU/L. None of the patients reported recurrent sinopulmonary infections. The difference in the number of patients with chronic sinopulmonary inflammatory diseases between both groups was not statistically significant ($p = 0.48$). Two patients with serum total IgE <2 kU/L (12%) and four patients with serum total IgE $\geq 2,000$ kU/L (24%) were diagnosed with atopic dermatitis ($p = 0.66$).

Discussion

The new finding of this small retrospective study is that chronic rhinosinusitis and asthma are present in adult patients with undetectable serum total IgE residing in inner-city Chicago, who seek medical care at two large, university-affiliated hospitals. We posit that indoor and outdoor air pollutants and/or aeroallergens in inner-city Chicago might influence the development of chronic sinopulmonary inflammatory diseases regardless of serum total IgE level [12].

The limitations of this retrospective study are obvious. The number of patients studied over a 5-year period was small given the prevalence of patients presenting with serum total IgE levels <2 and $\geq 2,000$ kU/L [17, 18]. In addition, both groups were not matched for age and sex and the extent of disease severity could not be compared due to

the small number of patients. Lastly, no other diagnostic laboratory data such as cellular inflammation in sputa or biopsy specimens or serum levels of proinflammatory cytokines and chemokines were available on these patients. Clearly, a prospective multicenter study comprising a larger number of patients with chronic rhinosinusitis and asthma and residing in inner-city Chicago is indicated to determine whether undetectable serum total IgE is a biomarker of distinct chronic rhinosinusitis and asthma phenotypes in this population.

Despite the well-established beneficial effects of IgE in humoral and antitumor immunity, the serum IgE level in healthy human subjects is very low relative to that of other circulating immunoglobulin classes due to reduced memory and activation responses of IgE-producing B cells [17, 18]. Importantly, the serum half-life of IgE is only a few hours compared to a half-life of days for other circulating immunoglobulin classes [17, 18]. In addition, several factors regulate serum total IgE level in the general population, including sex, age, race, environment, and seasonality [19–26]. Accordingly, serum total IgE level is variable in healthy individuals [17–26].

Current concepts suggest that isolated IgE hypogammaglobulinemia is a laboratory finding that does not necessarily correlate with clinical disorders [7, 9, 17, 18]. For instance, selective IgE deficiency was found in 0.8% of adult blood donors and in 3.1 and 1.3% of patients seen in allergic/immunologic and rheumatology clinics at the National Institutes of Health, respectively [7]. One of seven adult blood donors with selective IgE deficiency had a history of chronic rhinosinusitis. These investigators concluded that IgE deficiency does not predispose individuals to chronic sinopulmonary inflammatory diseases. Whether undetectable serum total IgE observed in our adult patients residing in inner-city Chicago is related in part to these factors, including limited production or accelerated catabolism and/or elimination of IgE, is uncertain.

Given that a high serum total IgE level is associated with common atopic diseases, most notably asthma [1–4], a monoclonal antibody against IgE (omalizumab) has been shown to be efficacious in a selected group of patients with allergic asthma [17, 18]. To this end, IL-4 and IL-13, cytokines produced by activated Th2 lymphocytes and B cells and present at increased levels in patients with allergic rhinitis and asthma, promote isotype class switching to IgE in B cells resulting in increased total serum IgE levels [17, 18]. Although IL-4 and IL-13 levels were not determined in our study, the results of this study show that 8 of 17 patients had asthma and chronic rhinosinusitis along with undetectable serum total IgE. These data suggest that IL-4-, IL-13-, and IgE-independent mechanisms underlie expression of both disorders in inner-city Chicago dwellers with undetectable serum IgE given

that their ongoing exposure to indoor and outdoor air pollution and aeroallergens is similar to that of patients with allergic rhinitis and asthma with exceedingly high ($\geq 2,000$ kU/L) serum total IgE level [2, 21, 23].

This notion is supported in part by the study of Pinto et al. [27] who showed that treatment with omalizumab for 6 months had only modest effects in patients with chronic rhinosinusitis. The results of this study contrast, however, with those reported from Tucson, AZ, an urban community located in an arid region of the southwestern US, where no physician-diagnosed asthma was reported among subjects with very low serum total IgE [12]. These data, coupled with studies reported from rural eastern Tennessee [5] and southeastern Michigan [6], suggest the presence of a distinct interplay between IgE and local environmental factors in the pathogenesis of chronic rhinosinusitis and asthma in inner-city Chicago residents. Conceivably, IgE may not be required for the development of chronic mucosal inflammation in these patients [2, 10, 11, 18, 25]. This hypothesis is supported in part by Palmer et al. [2] who showed that increased airway responsiveness is genetically distinct from atopy in an Australian population-based sample of 232 Caucasian nuclear families.

In summary, we found that chronic rhinosinusitis and asthma are diagnosed in adult patients with undetectable serum total IgE residing in inner-city Chicago. Whether undetectable serum total IgE is a biomarker of distinct chronic rhinosinusitis and asthma phenotypes in adult patients residing in inner-city Chicago remains to be determined.

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Conflict of interest The authors have no conflicts of interest to disclose.

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