

Prevalence of Allergen-Specific IgE Among Patients with Chronic Fatigue Syndrome

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ABSTRACT

The prevalence of atopy among patients having chronic fatigue syndrome (CFS) has been reported to be as high as 80% in published surveys of patients with this syndrome. However, many of the reports relied on self-assessment by patients for the presence of atopy or solely used total immunoglobulin E (IgE) levels to assess the likelihood of atopy. To more critically assess the presence of atopy among patients with CFS, testing was done for total IgE and allergen-specific IgE using the Pharmacia CAP system including 20 common allergens: trees (birch/oak/ash), grass (rye/blue), weeds (common/giant ragweed), molds (Penicillium/Aspergillus/Alternaria), dust mites (Dermatophagoides pteronyssinus/Dermatophagoides farinae), animal dander (cat/dog), and foods (egg white/milk/wheat/corn/peanut/shrimp). Testing of 50 patients having documented CFS indicated that 78% had total IgE < 100 IU/mL, among whom 26% had a positive test for allergen-specific IgE of class I or greater for one or more allergens. Among the 22% of CFS patients having a total IgE > 100 IU/mL, 73% had a positive test for allergen-specific IgE for one or more allergens. The most commonly positive allergens were dust mites (24–26%), whereas molds (0–6%) and foods (0–4%) were rarely positive. The overall frequency of positive results for the presence of allergen-specific IgE among CFS patients was 36%, not significantly different from the normal prevalence of these antibodies in the general population (20–35%). This assessment of the prevalence of allergen-specific IgE antibodies in patients with

CFS fails to support a potential association between CFS and atopy. (Allergy and Asthma Proc 23:35–39, 2002)

Chronic fatigue syndrome (CFS) is characterized by disabling fatigue, which is accompanied by a combination of nonspecific symptoms. The diagnosis of CFS is based on clinical manifestations and criteria; no definitive etiologic factor has been identified yet.^{1–4} It has been postulated that chronic inflammatory processes, viral infections, endocrine disturbances, psychiatric disorders, and/or organic changes in the central nervous system may be the cause of CFS.^{5–7} The prevalence of atopy among patients having CFS has been reported to be as high as 80% in published surveys of patients with this syndrome.^{8,9} However, many of the reports relied on patient self-assessments of atopy.

Overproduction of immunoglobulin E (IgE) is one of the characteristic features of atopy, which results in the presence of higher levels of total and allergen-specific IgE antibodies in the blood of patients who are allergic.¹⁰ Moreover, especially in patients having seasonal allergies, the concentration of allergen-specific IgE correlates well with disease activity, rising on an allergen exposure and decreasing during allergen-free periods.¹¹ A worse prognosis for allergic diseases is associated with a higher concentration of specific IgE detected in patients' sera.¹⁰ Therefore, detection of allergen-specific IgE in serum seems to be an objective and reliable indicator of allergy sensitization.

Several methods have been applied to evaluate allergen-specific IgE concentration in serum, including radio- and immunoassays.¹² The Pharmacia CAP system (Pharmacia Diagnostics Division, Kalamazoo, MI) is a very sensitive and specific method that recently has been found to have high precision, accuracy, and reproducibility in evaluation of specific and total IgE.¹²

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TABLE I

Allergen-Specific IgE Testing: Allergens Investigated

Allergen	Identity
T3	Common silver birch
T7	Oak
T15	White ash
G5	Rye grass
G8	Meadow grass; Kentucky blue
W1	Common ragweed
W3	Giant ragweed
M1	<i>P. notatum</i>
M3	<i>A. fumigatus</i>
M6	<i>A. alternata</i>
D1	<i>D. pteronyssinus</i>
D2	<i>D. farinae</i>
E1	Cat dander
E2	Dog epithelium
F1	Egg white
F2	Milk
F4	Wheat
F8	Corn
F13	Peanut
F24	Shrimp

In this study, the Pharmacia CAP system was used to test 50 sera from CFS patients for the evaluation of total IgE concentration as well as the allergen-specific IgE directed against common aeroallergens and food allergens.

MATERIALS AND METHODS

Fifty patients with a documented history of CFS were included in the study. They all fulfilled the CFS case definition criteria from 1994.³ All of them had been suffering from disabling fatigue for at least 6 months before the examination and had at least four of eight associated symptoms: sore throat, arthralgia of multiple joints, muscle pain, impaired memory or concentration, tender lymph nodes, headaches, nonrefreshing sleep, and postexertional malaise.

Venous blood was collected and centrifuged at 2500 rpm for 10 minutes to remove all cellular elements of the blood. Serum samples were stored at -20°C until tested. Both total and specific IgE levels were evaluated using the Pharmacia CAP system (Pharmacia Diagnostics) according to the manufacturer's instructions. Most frequently encountered allergens including common aeroallergens in the New England area and common food allergens were used for detection of specific IgE antibodies (Table I).

RESULTS

The mean total IgE level for the 50 CFS patients tested was within the age-normal limits (66.9 ± 90.5 IU/mL). Total IgE >100 IU/mL was shown in 11 out of 50 patients (22%) tested sera (subgroup A), while each of the remaining 39 patients (subgroup B) had total IgE levels <100 IU/mL.

Specific IgE to at least one allergen tested was detected in 18 of 50 CFS patients (36%). The presence of allergen-specific IgE at a concentration >0.35 IU/mL (class I or higher) to at least one allergen tested was detected in the sera of eight patients in subgroup A (73%). In the subgroup B—specific IgE, class I or higher to at least one of the allergens tested was found in 10 patients (26%). Generally, most of the specific IgE detected was directed toward aeroallergens with rare serum IgE reactivity to food allergens. From the total 20 allergens evaluated, specific IgE directed toward 14 allergens was detected. Food- and mold-specific IgE were uncommon, borderline value (0.35 IU/mL) for wheat allergen-specific IgE being found in one patient and no elevated specific IgE (below 0.35 IU/mL) was noted toward *Penicillium notatum*, egg white, milk, corn, or peanut allergens. Irrespective of the total IgE concentration, the most commonly detected allergen-specific IgE were those directed against *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. (Fig. 1) Thirteen out of 50 investigated sera reacted with *D. pteronyssinus* (26%) and 12 reacted with *D. farinae* (24%). In subgroup A, seven sera reacted with *D. pteronyssinus* and six sera re-

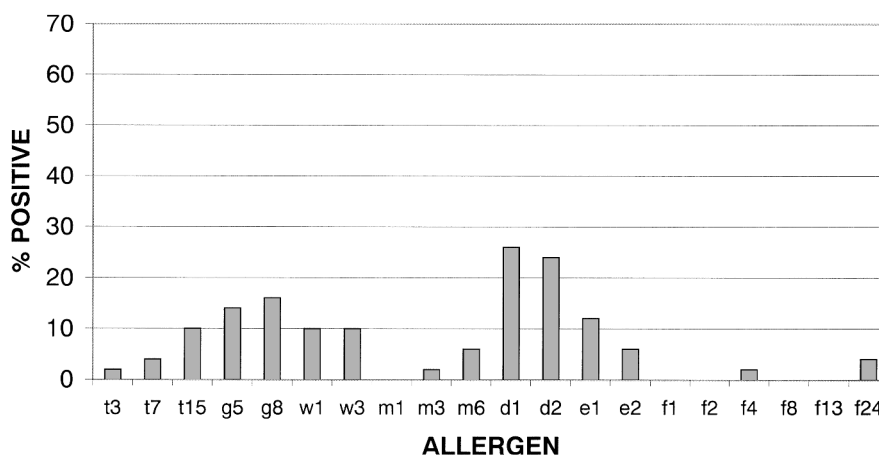


Figure 1. Frequency of allergen-specific IgE positivity for all CFS patients.

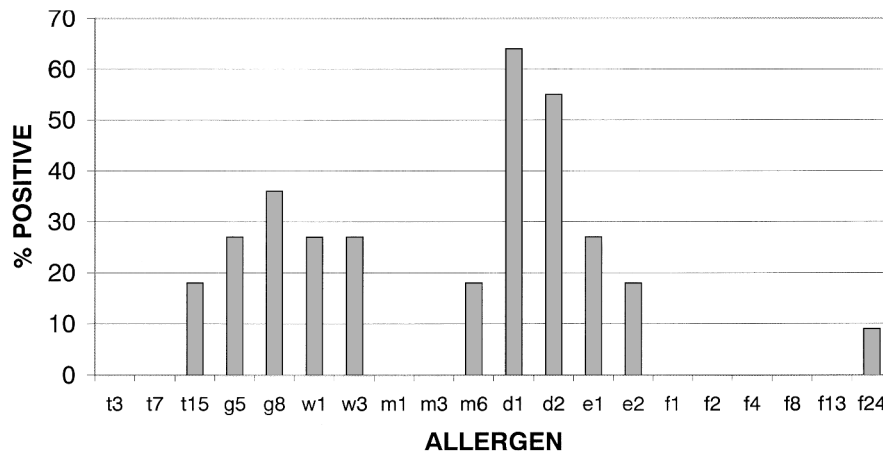


Figure 2. Frequency of allergen-specific IgE positivity for CFS patients with a total IgE of >100 IU/mL.

acted with *D. farinae* allergens (64 and 55%, respectively; Figs. 2 and 3). The highest mean concentration of allergen-specific serum IgE detected was against *D. farinae* (23.5 IU/mL) and *D. pteronyssinus* (19.9 IU/mL; Fig. 4). The prevalence of allergen-specific IgE directed toward other aeroallergens was <20%. The mean concentrations of allergen-specific IgE to the other aeroallergens in the sera of the 50 CFS patients were <10 IU/mL.

In summary, the overall frequency of elevated total IgE level and positive results for the presence of allergen-specific IgE among CFS patients were not significantly different than the normal prevalence of these antibodies found in the general population.¹³⁻¹⁵

DISCUSSION

During the last 20 years, several studies reported an increased prevalence of atopy among patients with CFS.^{8,9,16,17} The etiology of CFS has not yet been clarified so these reports suggest an attractive hypothesis concerning the role of allergy in the genesis of CFS.

There is no perfect test for the presence of allergy; therefore, several methods have been used to help discriminate atopic persons from nonatopic persons.^{11,18} Overpro-

duction of IgE is a well-known stigma of atopy. It has been shown that the best discrimination between atopic and nonatopic populations was seen at a total IgE level of 100 IU/mL, although significant overlap in both populations was observed.¹⁹ Therefore, a higher percentage of atopic persons in any population should be associated with a higher mean total serum IgE, which in this way can be used as a screening test for atopy. In one study, Orgel and coworkers compared levels of total IgE with incidence of atopy in two populations of children living in the United States.²⁰ The authors found a higher incidence of atopy in Filipino children as compared with the white group (48% versus 25%). In the former group mean total IgE was 227 IU/mL, which was significantly higher than in the latter group in which mean total IgE was 69 IU/mL.²⁰ This study emphasized the value of total IgE as an accurate marker for atopy in the population studies. Our results do not allow us to show higher mean total IgE in the studied group of 50 patients with CFS than in the general population, which in this study does not support the hypothesis of increased prevalence of atopic disorders among CFS patients. We investigated further the possibility that CFS patients with atopy may represent a subgroup of atopic individuals with a

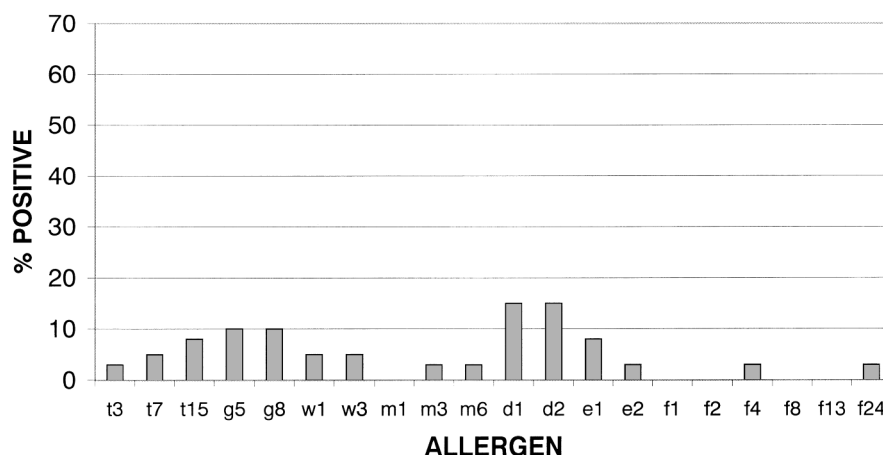


Figure 3. Frequency of allergen-specific IgE positivity for CSF patients with a total IgE of <100 IU/mL.

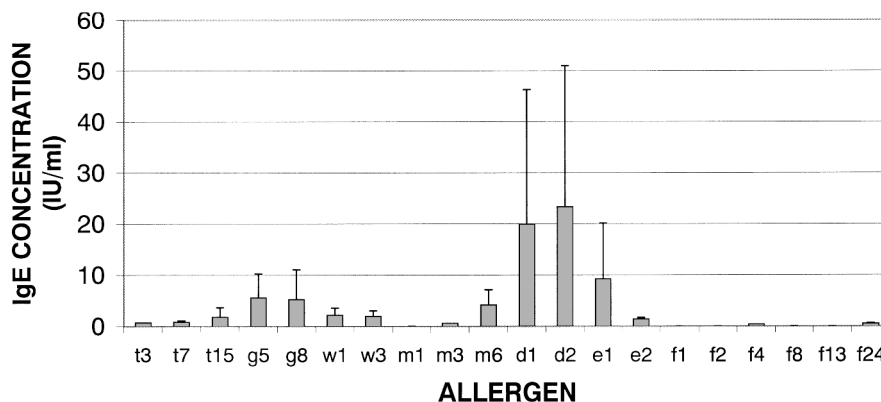


Figure 4. Mean allergen-specific IgE concentration of all CSF patients.

lower level of total IgE. To address this issue, evaluation for the presence of allergen-specific IgE was performed. Recently, new techniques have allowed detection of allergen-specific IgE in the serum with high accuracy and precision making these tests as reliable as skin-prick tests in the diagnosis of some allergen-mediated diseases like rhinitis and asthma.^{11,18} Serum concentrations of allergen-specific IgE have been shown to correlate well with disease activity, with higher allergen-specific IgE levels connected with a worse prognosis for the development of allergen-mediated symptoms.^{10,11} We were not able to find an increased prevalence of allergen-specific IgE antibodies in the sera of CFS patients when compared with the reported prevalence of allergen sensitization in the general population.^{13–15}

Unfortunately, most studies reporting a higher prevalence of atopy in CFS patients are limited by the low number of studied patients and by application of a subjective diagnosis of atopy often based solely on the patient history.^{9,16} In a comparative study of patients having CFS, allergic rhinitis, depression, and normal controls, Borish and coworkers tried to estimate the incidence of atopy by means of skin-prick tests and evaluated production of certain cytokines by the peripheral blood mononuclear cells of these.⁸ Borish was able to establish that the production of tumor necrosis factor α (TNF- α), interferon α (IFN- α), interleukin 1 β (IL-1 β), and IL-10 did not differ between patients who were allergic and patients who had CFS. Interestingly, the high incidence of atopy as defined by positive skin test results was observed not only among CFS patients but also among depressed patients raising the possibility of some bias during patient selection, because referring the patients to a large academic allergy clinic may have biased the patient population chosen for study in this investigation.⁸ Another problem of the report was the low number of studied patients—18 patients in the CFS group and 12 patients in the depression group, the limited study size diminishing the likelihood that these patients were truly representative of all CFS patients.⁸ In a study of 113 patients with CFS, Baraniuk and coworkers found symptoms of allergic rhinitis in 35 CFS patients (31%), although the diagnosis was based mainly on subjective patient reports.²¹ Further investiga-

tions of a possible etiologic relationship between atopy and CFS are provided by studies investigating the effect of antiallergic treatments on the course of CFS. Sternberg and coworkers analyzed the effect of a selective H1 antagonist terfenadine on CFS-related symptoms in a double-blind placebo-controlled study.⁹ No beneficial effect of terfenadine was reported in patients with CFS. Similarly, in a double-blind, placebo-controlled cross-over study, Kaku-manu and coworkers evaluated the effect of topical intra-nasal steroids on CFS symptoms in patients suffering from CFS and rhinitis. No improvement was found in the severity of CFS-associated symptoms including fatigue, muscle pain, and daytime sleepiness.²² Both of these studies indicated that pharmacologic therapy designed to antagonize or limit the action of allergic mediators does not seem to impact the symptoms of CFS.

Our finding of the prevalence of allergen-specific IgE in CFS patients occurring in the same range as those found in the general population fails to support the potential association between CFS and atopy. Our study indicates that atopy can coexist with CFS, which also may explain why different CFS-studied populations differ so markedly in the incidence of atopy. Moreover, the participation of IgE-mediated reactions in the pathogenesis of symptoms observed in CFS seems unlikely.

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