

Original article

Allergic asthma in patients with common variable immunodeficiency

Background: Many patients with common variable immunodeficiency (CVID) have a clinical history suggestive of allergic respiratory disease. However, in such individuals, the prevalence of asthma and the role of atopy have not been well established. The objective of this study was to evaluate pulmonary function and identify asthma in patients with CVID. We also investigated the role of IgE as a trigger of asthma in these patients.

Methods: Sixty-two patients diagnosed with CVID underwent spirometry, as well as skin prick testing and *in vitro* determination of serum-specific IgE levels for aeroallergens, together with bronchial provocation with histamine and allergen.

Results: The most common alteration identified through spirometry was obstructive lung disease, which was observed in 29 (47.5%) of the 62 patients evaluated. Eighteen (29.0%) of the 62 patients had a clinical history suggestive of allergic asthma. By the end of the study, asthma had been diagnosed in nine (14.5%) patients and atopy had been identified in six (9.7%). In addition, allergic asthma had been diagnosed in four patients (6.5% of the sample as a whole; 22.2% of the 18 patients with a clinical history suggestive of the diagnosis).

Conclusion: In this study, CVID patients testing negative for specific IgE antibodies and suspected of having allergic asthma presented a positive response to bronchial provocation tests with allergens. To our knowledge, this is the first such study. When CVID patients with a history suggestive of allergic asthma test negative on traditional tests, additional tests designed to identify allergic asthma might be conducted.

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Common variable immunodeficiency (CVID) is a primary humoral immunodeficiency that displays multiple phenotypes, all of which feature hypogammaglobulinemia. The diagnosis of CVID cannot be made until other known causes of hypogammaglobulinemia have been excluded. Although CVID is considered to be a humoral immunodeficiency, approximately 40% of CVID patients have low T-cell counts or abnormal T-cell function (1).

The most common clinical manifestations of CVID are recurrent and chronic bacterial infections, especially of the respiratory and gastrointestinal tracts, and there is a high prevalence of autoimmune phenomena and cancer among CVID patients (1–4). The standard treatment for CVID is periodic infusion of intravenous immunoglobulin, which reduces the prevalence of recurrent infections (2, 3, 5). As the diagnosis is frequently established at a later stage, patients with CVID can also present bronchiectasis and other pulmonary complications (2, 5).

Obstructive diseases, such as asthma and bronchiectasis, are present in more than 50% of CVID patients (5).

The prevalence of bronchiectasis in these patients is high (33–73%), especially when more sensitive investigation techniques are used, computed tomography of the chest being preferable to chest X-ray (5–7). Silent progression of pulmonary alterations has been reported, even in patients receiving adequate intravenous gamma globulin replacement therapy (7).

As recurrent or chronic pyogenic sinopulmonary infections constitute the most common clinical manifestation, pulmonary function testing should be regarded as a routine exam (2, 5).

Asthma is highly prevalent worldwide and occurs in approximately 10% of the Brazilian population. Asthma is defined based on clinical findings and pulmonary function test results (8). Airflow obstruction that is reversible and bronchial hyperresponsiveness are features that support a diagnosis of asthma (8).

In one study evaluating respiratory comorbidities in CVID patients, the prevalence of asthma was found to be 15% (9). In CVID patients, asthma can be masked by recurrent respiratory infections. However, asthma

patients are more susceptible to protracted respiratory infections, which might delay a possible diagnosis of humoral immunodeficiency.

Similar to what is seen in IgA deficiency, the mucosal immunodeficiency observed in CVID patients could facilitate the development of allergic reactions to aeroallergens, inflammation, bronchial hyperresponsiveness, and consequently, asthma (10).

Studies on IgE biology have indicated a correlation between serum IgE concentrations and IgE concentrations in other body fluids. However, some studies have demonstrated that allergen-specific IgE can be present in certain body fluids, despite normal serum levels of specific IgE (11).

Many patients with CVID have a clinical history suggestive of allergic respiratory disease. However, the role that atopy plays in these individuals has not been well established, as levels of total IgE or specific IgE are often low. In such patients, reports of rhinitis and asthma can be confused with a history of recurrent respiratory infections.

This study had multiple objectives: to evaluate pulmonary function in patients with CVID; to identify asthma in those same patients; and to investigate the role that IgE plays as a trigger of asthma in patients with CVID.

Methods

This study included 62 patients with a clinical history and diagnosis of CVID who were being monitored at our Primary Immunodeficiency Outpatient Clinic. The study was carried out between March of 2007 and November of 2008. All patients met the criteria for a diagnosis of CVID, presenting serum levels of IgG, IgA and IgM that were below two standard deviations of the age-specific normal value, together with an inability to synthesize specific antibodies (1). Other causes of immunodeficiency were ruled out. Patients were informed of the study procedures, including the proposed tests and the need of hospitalization. All participating patients then gave written informed consent.

Study design

Clinical histories were taken, and all patients underwent physical examination. Subsequently, the patients were submitted to spirometry and skin prick tests for the investigation of specific IgE for aeroallergens, as well as determination of serum specific IgE levels using the ImmunoCAP system (Pharmacia Diagnostics, Uppsala, Sweden).

All patients who accepted to perform bronchial challenges, and did not present exclusion criteria, were hospitalized and underwent three bronchial provocation tests: with histamine on day 1; with an allergen on day 2; and again with histamine on day 3 (the final day of the hospitalization). Exclusion criteria for bronchial provocation were: FEV₁ < 70%; severe asthma exacerbation during the last 6 months; systemic corticosteroid administration during the last month; respiratory infection during the last month; inability to perform lung function test; noncontrolled systemic severe diseases; pregnancy.

Patients were classified as having asthma if reporting a clinical history suggestive of asthma, as described in the 2006 Global Initiative for Asthma statement, and presenting bronchodilator-responsive obstructive lung disease (OLD) (lung function test) or a positive response to bronchial provocation with histamine or with a specific allergen (12).

Patients were considered atopic if presenting a clinical history suggestive of allergic respiratory disease (rhinitis and asthma symptoms associated with aeroallergen exposition; early onset of symptoms; and a personal/family history of atopy), as described by the World Allergy Organization, and presenting evidence of specific IgE antibodies (skin prick test or ImmunoCAP) or a positive response to bronchial provocation with allergen (13).

Skin prick test and serum levels of specific IgE

We used a modified version of the Pepys skin prick test, in duplicate (14). The test battery was carried out using extracts obtained from Alergia Clínica Laboratorial e Comércio Ltda (São Paulo, Brazil) and including the following allergens: *Dermatophagoides pteronyssinus* (Der p); *Dermatophagoides farinae*; *Blomia tropicalis*; *Cladosporium herbarum*; *Alternaria alternata*; *Penicillium notatum*; *Aspergillus fumigatus*; *Canis familiaris*; *Felis domesticus*; *Lolium perenne*; *Periplaneta americana*; and *Blatella germanica*.

The ImmunoCAP technique used in this study included the same allergens used in the skin prick tests (15). The ImmunoCAP test result was considered positive if IgE levels were higher than 0.35 kU/l.

Spirometry

Spirometry was performed using a Koko spirometer (Ferraris Respiratory, Louisville, CO, USA). All spirometry tests were conducted between 7:00 am and 9:00 am, always by the same technician. The spirometry techniques employed and the method of interpreting the results were those set forth in the American Thoracic Society/European Respiratory Society consensus of 2005 (16). Spirometry findings were therefore classified as follows: normal; OLD; or suggestive of restrictive lung disease (RLD). A positive response to bronchodilator agents was defined as an increase of at least 12% and 200 ml in forced expiratory volume in 1 s (FEV₁) or forced vital capacity.

Bronchial provocation test with histamine

All bronchial provocation tests were performed, in a respiratory investigation chamber, between 8:00 am and 10:00 am on the designated days. The first nonspecific (histamine) bronchial provocation test was carried out on the morning of day 1 of hospitalization, and the second nonspecific bronchial provocation test was carried out on day 3 of hospitalization.

The technique used for the bronchial provocation tests was based on that described by the American Thoracic Society in 2000 (17, 18). We used six different histamine dilutions (0.065; 0.25; 1; 4; 10 and 16 mg/ml). A dosimeter was used for nebulization. The first inhalation was performed with saline, and subsequent inhalations were with the abovementioned graded histamine dilutions. The FEV₁ was determined at 30 and 90 s after the end of each inhalation series. Histamine inhalations continued until a reduction in FEV₁ ≥ 20% (in relation to the FEV₁ determined after saline inhalation) was observed or until the maximum concentration of 16 mg/ml was reached.

The test outcome was considered normal when the provocative concentration of histamine that induced a 20% decrease in FEV₁ (histamine PC₂₀) was > 16 mg/ml. The test outcome was considered positive when the histamine PC₂₀ was ≤ 8 mg/ml; and an intermediate result was defined as a histamine PC₂₀ between 8 and 16 mg/ml (17–19).

The aim of the second bronchial provocation test with histamine, after the specific bronchial provocation test with Der p allergen, was to identify a possible increase in baseline bronchial hyperresponsiveness after allergen inflammation.

Specific bronchial provocation test with *Dermatophagoides pteronyssinus*

The technique used for specific bronchial provocation test with Der p has previously been described (19). We chose Der p because it is the allergen that is most common in our environment, as well as because monosensitization to an agent other than Der p is uncommon (20).

The specific bronchial provocation test, which required approximately 2.5 h to complete, was performed on day 2 of hospitalization, beginning between 7:30 am and 9:00 am.

We used the Der p extract at a concentration of 0.95 mg/ml (prick test concentration). In patients presenting skin reactivity to Der p, the initial dilution used in the bronchial provocation test was equivalent to two dilutions lower than the dilution provoking a 2 × 2 mm wheal on the skin prick test. In patients with negative skin prick test results, the Der p extract was used at an initial dilution of 1 : 256. To limit test duration and ensure patient safety, the maximum dilution employed was 1 : 8, and no more than six dilutions were used.

As in the histamine provocation test, we used a nebulizer with a dosimeter, and the initial inhalation was of saline. For each Der p dilution used thereafter, five inhalations were administered. The FEV₁ was determined at 90 s and 20 min after each series. The Der p bronchial provocation test was stopped when the maximum concentration was reached or when FEV₁ dropped to ≥15% of that determined after saline inhalation. This drop characterized a positive test.

The response to the specific bronchial provocation test was also considered positive when there was a ≥20% post-test log drop in histamine PC₂₀ (difference between PC₂₀ measurements performed before and after specific bronchial test) (21).

Peak expiratory flow

Peak expiratory flow (PEF) was measured using a Mini-Wright flow meter (Clement Clarke, Harlow, UK) and was determined hourly for 10 consecutive hours after the bronchial provocation tests performed on days 1 and 2.

Statistical analysis

The unpaired Student's *t*-test was used to compare independent samples. The chi-square test was used to evaluate differences between groups in terms of gender, skin prick test result, serum concentration of specific IgE and spirometry parameters.

In the evaluation of bronchial provocation test results, we considered all FEV₁ measurements and a regression analysis was performed to determine the PC₂₀ for each patient. Changes in PC₂₀ histamine were analyzed using logarithmic transformation and Spearman's correlation coefficient was used to evaluate the samples.

Results

The study sample included 62 patients (30 men and 32 women) in outpatient treatment for 1–30 years (mean, 6.5 years). Ages ranged from 18 to 74 years (mean, 35.9 years), and all patients were receiving gamma globulin replacement therapy. Age at symptom onset, age at diagnosis and the interval between the two are shown in Table 1.

Of the 62 patients, 29 (46.7%) had a clinical history suggestive of asthma. Of those 29 patients, 18 (29.0% of the sample) were under treatment with asthma controller medication. Twenty-seven patients (43.5%) had a clinical history of atopy, and 18 of those 27 patients (29.0% of the sample) also had a clinical history suggestive of allergic asthma.

Total IgE in serum was abnormal (> 100 IU/ml) in only two of the patients (both male; 159 and 1450 IU/ml), one of whom had a history of allergic rhinitis. Among the remaining 60 patients, total IgE was between 4 and 16 IU/ml in 18, whereas it was undetectable in 42 (68%).

The skin prick test for aeroallergens was performed in 61 of the 62 participating patients and yielded two positive results. Both of the patients testing positive had a history of allergic rhinitis; one had a history suggestive of allergic asthma and had presented IgA deficiency prior to developing CVID. Using the ImmunoCAP method, we found the serum concentration of specific IgE to Der p in those same two patients to be 0.56 and 3.23 kU/l.

All but one of the patients underwent spirometry. Of those 61 patients, 25 (41%) presented normal spirometry results, 29 (47.5%) presented findings of OLD, and seven (11.5%) presented findings suggestive of RLD. Table 2 demonstrates the severity of OLD based on FEV₁.

Of the 29 patients with a history suggestive of asthma, 19 (65.5%) were diagnosed with OLD, and asthma was confirmed in six (20.7%), all of whom also responded to the administration of a bronchodilator.

Table 1. Characteristics of patients with common variable immunodeficiency (CVID) monitored at the *Hospital das Clínicas* of the School of Medicine of the University of São Paulo

Characteristic	Men (<i>n</i> = 30)	Women (<i>n</i> = 32)	Total (<i>n</i> = 62)
Mean age at study outset (years)	35.7 ± 14.4	36.1 ± 13.8	33.0
Mean age at symptom onset (years)	14.0 ± 9.8	13.5 ± 12.2	13.8
Mean age at diagnosis (years)	27.6 ± 13.4	29.8 ± 13.4	28.7
Mean time to diagnosis (years)	13.6 ± 13.4	16.3 ± 9.8	15.0

Table 2. Distribution of obstructive lung disease

OLD severity (FEV ₁)	Men	Women	Total
Mild ($\geq 70\%$)	9	6	15
Moderate (69–60%)	2	4	6
Moderately severe (59–50%)	0	0	0
Severe (50–35%)	2	2	4
Extremely severe ($\leq 34\%$)	2	2	4
Total	15	14	29

OLD, obstructive lung disease; FEV₁, forced expiratory volume in 1 s.

By the end of the study, 62 patients had undergone testing for serum IgE (total and specific) and 61 had been submitted to skin prick testing and spirometry.

In many cases, it was not possible to perform all three bronchial provocation tests, as most of the patients had severe respiratory disease and others were unable to remain in the hospital for 3 days. Therefore the full battery of bronchial provocation tests was administered in only 15 patients, five of whom had a history suggestive of allergic asthma.

During the initial phase of the nonspecific bronchial provocation test with histamine, asthma was confirmed in three patients with a history suggestive of asthma. One of those patients presented spirometry results consistent with OLD and was responsive to bronchodilator administration.

During the bronchial provocation test with Der p, none of the patients presented a drop in FEV₁ $\geq 15\%$, at any dilution. Serial peak expiratory flow measurements performed after the specific bronchial provocation test did not detect any late phases of the allergic reaction.

Nevertheless, during the third bronchial provocation test, which was performed with histamine on day 3 of hospitalization, we observed a difference between the patients with a history suggestive of allergic asthma and those without such a history (Fig. 1). After the third bronchial provocation test, four of the five patients with a history suggestive of allergic asthma had a drop in FEV₁ $> 20\%$ when compared with the result obtained during the first histamine test. This was a statistically significant difference in comparison with the results obtained for the patients without a history suggestive of allergic asthma ($P = 0.0012$).

In accordance with the criteria of this study, asthma was confirmed in nine of the 29 patients with a history suggestive of asthma, and four of those nine were diagnosed with allergic asthma (Table 3).

Discussion

This study was carried out to increase the understanding of the pathophysiology and diagnosis of respiratory atopy in patients with CVID. In comparison with the findings of most such studies, our patients were younger

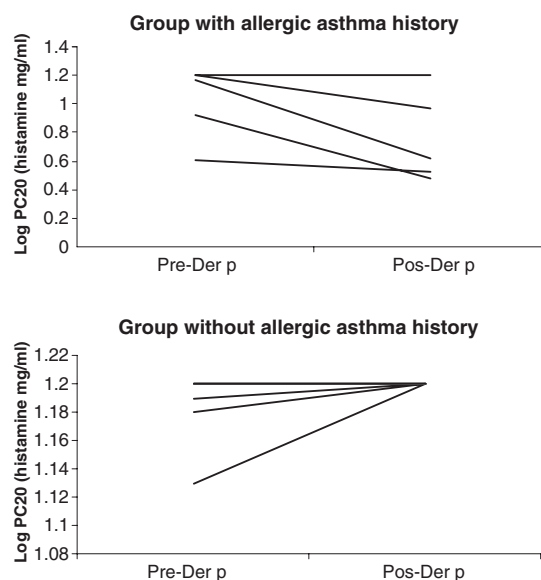


Figure 1. The log histamine PC₂₀ values before and after bronchial provocation with Der p in the two groups of patients (those suspected of having allergic asthma and those not under such suspicion).

at symptom onset and the diagnosis of CVID was established earlier. Nevertheless, the interval between the onset of symptoms and the diagnosis was longer (2, 3, 22, 23).

In brief, we found that 46.7% of the patients evaluated had a history suggestive of asthma, 43.5% had atopy, and 29.0% had a history suggestive of allergic asthma. Of the 29 patients with a history suggestive of asthma, only six had OLD and presented a positive bronchodilator response. Bronchial provocation testing was performed in 15 patients, and four of the five patients with a history suggestive of allergic asthma presented a positive response.

It is difficult to evaluate asthma and atopy in patients with CVID. Some patients present respiratory symptoms that might represent only the infectious complications

Table 3. Asthma and allergic asthma diagnosis

Patient	Diagnosis	OLD with BR	AHR (histamine)	SBC
1	Asthma	Positive	Negative	Negative
2	Asthma	Positive	Negative	Negative
3	Asthma	Positive	Negative	Negative
4	Asthma	Positive	Negative	Negative
5	Asthma	Positive	Negative	Negative
6	Allergic Asthma	Positive	Positive	Positive
7	Allergic Asthma	Negative	Positive	Positive
8	Allergic Asthma	Negative	Positive	Positive
9	Allergic Asthma	Negative	Negative	Positive

OLD with BR, obstructive lung disease with bronchodilator response; AHR, airway hyperresponsiveness; SBC, specific bronchial challenge.

of CVID or might actually be manifestations of respiratory allergy. Unfortunately, late diagnosis is characteristic of this immunodeficiency. In one study, it was reported that a case of panhypogammaglobulinemia was treated as allergic respiratory disease for 40 years before the diagnosis of immunodeficiency was made (24).

In this study, spirometry revealed that most (59.0%) of the patients presented obstructive or restrictive alterations. Pulmonary function testing should be a routine procedure, as 36.1% of the symptom-free patients presented abnormal spirometry results and others underestimated their respiratory symptoms.

When we consider clinical history alone, the prevalence of asthma in patients with CVID might be overestimated, as some individuals present respiratory symptoms as a result of repeated infections and cicatricial alterations. Therefore, some patients without asthma might be receiving asthma treatment.

We found spirometry and bronchial provocation testing to be useful for the confirmation of a diagnosis of asthma. At the study outset, we questioned whether pulmonary manifestations of CVID *per se* would result in airway inflammation and hyperresponsiveness. Such hyperresponsiveness was not confirmed. However, the fact that few patients suspected of having asthma presented OLD with a positive bronchodilator response in spirometry and positive bronchial provocation with histamine might be a consequence of the treatment with inhaled anti-inflammatory drugs that some patients were receiving.

Our difficulty in determining specific IgE using traditional methods might be related to the extremely low IgE concentrations observed in patients with CVID. Nevertheless, a number of studies have evaluated the production of local specific IgE, even in situations in which total or specific serum IgE were normal. (11, 25, 26).

For decades, bronchial provocation tests have been extensively used as a model for asthma investigation. These tests made a significant contribution to the understanding of asthma pathophysiology and of the mechanisms involved in the effects of asthma medication (27).

Bronchial provocation tests with allergens frequently result in immediate and late reactions, as well as inducing nonspecific bronchial hyperresponsiveness, which increases 2–3 h after allergen exposure, peaking in intensity at 24 h after the exposure. The bronchial hyperresponsiveness can persist for days or weeks (21,28,29).

The aim of this study was to evaluate local allergy to a relevant allergen, using specific bronchial provocation testing. Therefore, we focused on indirect investigation of local specific IgE through specific bronchial provocation tests.

Despite the negative results obtained with the methods routinely used in atopy investigations, the specific bron-

chial provocation test with allergen employed in this study detected an increase in bronchial responsiveness in four (80.0%) of the five patients with a history suggestive of allergic or atopic asthma.

Our results suggest that an IgE-mediated response could play a role in the pathogenesis of asthma in patients with CVID. However, we were unable to demonstrate the participation of this antibody in the inflammatory process, as we did not collect the bronchial material that would be needed to characterize such participation. Otherwise, the absence of an immediate response to the bronchial provocation test with Der p, followed by positive late response, might represent a form of allergic asthma with a Th2 inflammatory profile, albeit through IgE-independent mechanisms. Animal models have been used to study the development of allergen-induced eosinophilic inflammation and bronchial hyperresponsiveness without IgE involvement (30–32). In such situations, there is an inflammatory process that includes cell activation, synthesis of mediators (such as IL-4, IL-5, IL-13, eotaxin and RANTES) and expression of adhesion molecules. However, this does not preclude the knowledge that IgE plays an important role in triggering and amplifying Th2-driven allergic reactions.

One patient, despite having a history suggestive of allergic asthma, did not present a positive response to bronchial provocation with Der p. This might be because the patient had been sensitized to an aeroallergen other than Der p, because the quantity of allergen was not sufficient to trigger symptoms, or because the regular asthma medication had been discontinued only 3 days prior to the test (16, 18, 33–35).

By the end of this study, asthma had been confirmed in nine (14.5%) of the patients with CVID, whereas atopy had been confirmed in six (9.7%), and allergic asthma had been confirmed in four (6.5%). The four patients diagnosed with allergic asthma corresponded to 22.2% of 18 patients suspected of having allergic asthma and to 80% of the five patients with a history suggestive of allergic or atopic asthma who were able to complete the investigation.

To our knowledge, this is the first time that a positive response to bronchial provocation test with allergen has been reported in CVID patients suspected of having allergic asthma and presenting negative results on specific IgE investigations. We also found OLD to be the most common spirometry alteration (in 47.5%), and that, in the majority of cases, OLD was accompanied by asthma. However, OLD was also observed in patients with no history of asthma, some of whom also presented bronchiectasis, a common complication in such patients. Therefore, the evaluation of allergic asthma in CVID is feasible in patients with a history suggestive of allergic asthma and testing negative on traditional tests.

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