

Can patients with common variable immunodeficiency have allergic rhinitis?

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ABSTRACT

Background: Rhinosinusitis is highly prevalent in patients with common variable immunodeficiency (CVID), and probably allergic rhinitis (AR) may be masked by a history of repeated respiratory infections. The diagnosis of AR is based on the patient's symptoms and detection of specific immunoglobulin E (IgE) to aeroallergens. This study was designed to identify rhinitis of probable allergic cause in patients with CVID.

Methods: This study included 72 adult CVID patients. The patients were divided into three groups according to their history: suggestive of AR, nonallergic rhinitis, and without rhinitis. They were tested for total and specific IgE (in vivo and in vitro).

Results: The patients' mean age was 38.2 years. A history of chronic rhinitis was observed in 59 (81.9%) of the cases, 31 of which (43%) had a history suggestive of AR. Patients with a history of rhinitis (whether allergic or nonallergic) presented an earlier onset of symptoms and diagnosis of CVID. Total IgE was undetectable in 86.1% of patients. AR was confirmed by detection of specific IgE to aeroallergens in only 5.6% of the patients.

Conclusion: In CVID patients, chronic rhinitis may be allergic, because many have personal and family histories suggestive of atopy. However, in this study, allergy was confirmed by specific IgE detection in only 5.6% of cases. CVID patients with a history suggestive of AR commonly present negative results on traditional testing, so additional experiments may be necessary. One suggestion for the investigation of AR in CVID patients would be nasal provocation with the most prevalent allergens.

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Common variable immunodeficiency (CVID) is a primary immunodeficiency classified as a predominantly antibody deficiency.^{1,2} It is characterized by the inability to produce quantitative and qualitative immunoglobulins.^{1–3}

This immunodeficiency is characterized by hypogammaglobulinemia, and one of the main manifestations is recurrent or chronic bacterial infections (mainly sinopulmonary).^{4,5}

Although infectious or recurrent pyogenic rhinosinusitis is very often seen in humoral immunodeficiencies,^{5–7} allergic and nonallergic rhinitis (NAR) are associated with persistent rhinosinusitis.^{8,9}

Rhinitis is an inflammation of the nasal mucosa characterized by the presence of symptoms such as nasal obstruction, rhinorrhea, sneezing, postnasal drainage, and nasal itching.^{10,11} Allergic rhinitis (AR) is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose.¹⁰

AR is a serious disease because of several factors, such as high prevalence, major impact on quality of life, and economic status.¹⁰ Its prevalence in Europe is ~20%^{10,12} and in Brazil it varies from 7 to 25% of the population.^{10,11}

The diagnosis of AR is based on clinical history, presence of personal and/or family history of atopic diseases, and detection of specific IgE for environmental allergens through skin-prick test or *in vitro* assay.¹⁰

Symptoms of chronic NAR can be similar to those of AR and triggering causes include infections, hormonal disorders, medications, anatomic defects, and physical agents.^{6,10,13}

Rhinitis is an independent risk factor for the development of asthma;

thus, asthma develops more commonly in patients with rhinitis than in those without the disease.^{10,14,15}

Another common manifestation is the association between rhinitis and sinusitis, and considering that the two diseases coexist in most individuals, the most appropriate term would be rhinosinusitis.^{10,16} According to the consensus, rhinosinusitis is considered chronic when it lasts >12 weeks despite appropriate drug treatment.^{6,16}

Patients with chronic rhinosinusitis may have a high frequency of specific antibody deficiency, which may be an unrecognized contributor to the prevalence and severity of illness and the failure of the medical treatment for this disease.¹⁷

The early diagnosis and treatment of AR or NAR is, therefore, important, to minimize possible complications such as asthma and rhinosinusitis. AR or rhinosinusitis may be masked by the infectious variety, which is a common manifestation in CVID patients, even in those on intravenous immunoglobulin therapy.^{15,18,19}

Considering that the majority of CVID patients do not produce IgE,^{20,21} it is noteworthy that the detection of specific IgE to environmental allergens, as a diagnostic criterion of AR, is not feasible. Thus, the objective of this study was to identify and characterize rhinitis of probable allergic cause in CVID patients.

METHODS

Patients

This was an observational and cross-sectional study involving adult CVID patients of both genders who were followed up at the Primary Immunodeficiency Outpatient Clinic of the Division of Clinical Immunology and Allergy, University of São Paulo, from January 2009 to December 2011.

The diagnosis of CVID was established in accordance with the international guideline criteria, *i.e.*, reduced levels of IgG and IgA and/or IgM, poor response to vaccines, and exclusion of other causes of hypogammaglobulinemia.^{3,22} All patients were undergoing intravenous immunoglobulin replacement therapy.

The study was approved by our local Human Research Ethics Committee, CAPPesq (Ethics Committee for Analysis and Research Projects), of the Medical School of the University of São Paulo. All the patients signed the informed consent form and all were assessed by

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Table 1 Chronologic characteristics of patients with CVID

Chronologic Characteristics	Male (n = 35)	Female (n = 37)	Total (n = 72)
Mean age at study onset (yr)	37.3 (SD = 13.9)	38.9 (SD = 13.5)	38.2 (SD = 13.6)
Mean age at onset of symptoms (yr)	15.2 (SD = 10.6)	12.5 (SD = 10.8)	13.8 (SD = 10.7)
Mean age at diagnosis (yr)	27.5 (SD = 12.1)	29.7 (SD = 12.9)	28.6 (SD = 12.5)
Mean time to diagnosis (yr)	12.3 (SD = 12.4)	17.2 (SD = 11.2)	14.8 (SD = 12.0)

CVID = common variable immunodeficiency.

the same physician. Patients were classified according to the presence or absence of rhinitis.

Clinical histories were recorded, and all of the patients underwent physical examination. Subsequently, the patients were submitted to *in vivo* (skin-prick test) and *in vitro* tests for the investigation of specific IgE for aeroallergens.

Chronic rhinitis is considered after acute rhinitis that lasts ≤ 1 week and usually presents a viral etiology or acute exacerbation of AR has been excluded.²³

Clinically, AR was considered when patients presented with nasal discharge, sneezing, nasal itching, and nasal obstruction associated with exposure to airborne allergens and in the absence of infectious symptoms.^{10,11,24} The diagnosis of NAR was based on the presence of rhinorrhea, sneezing, nasal obstruction, and/or itching nose that occurred on ≥ 2 consecutive days for >1 hour on most days,¹⁰ with no association with exposure to aeroallergens and/or the presence of infections.

Infectious rhinosinusitis was considered recurrent and associated with the onset of immunodeficiency symptoms, in patients with CVID and rhinitis, when it occurred more frequently than four times a year.¹⁶

Asthmatic patients were diagnosed according to the Global Initiative for Asthma guidelines.²⁵ Patients were interrogated about the frequency of recurrent rhinosinusitis or pneumonia, as well as diarrhea, as an initial manifestation of the CVID, before the diagnosis was established.

After the initial interview, these CVID patients were classified in three groups: the first included subjects with a history compatible with AR, the second with probable NAR, and the third group included patients without chronic rhinitis.

Total and Specific IgE

All patients were tested for total and specific IgE. Quantification of total IgE was performed by nephelometry and normal values were considered as being those of up to 100 IU/mL.

All patients were tested for specific IgE *in vivo* and/or *in vitro*.

The search for specific IgE *in vivo* was performed by skin-prick tests, in duplicate.²⁶ The test was performed using biological equivalent unit standardized and purified extracts obtained from ALC (ALC Alergia Clínica Laboratorial e Comércio Ltda, São Paulo, Brazil), including the following allergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, *Cladosporium herbarum*, *Alternaria alternata*, *Penicillium notatum*, *Aspergillus fumigatus*, *Canis familiaris*, *Felis domesticus*, *Lolium perenne*, *Periplaneta americana*, and *Blattella germanica*. The test was considered positive in the presence of papules of 3×3 mm greater than the negative control.

Quantification of serum-specific IgE for the same allergens as used for the skin-prick test was performed by immunofluorescence and followed the manufacturer's recommendations (ImmunoCAP system; Phadia, Uppsala, Sweden).²⁷ The test was considered positive when values of >0.35 kU/L were obtained.

Statistical Analysis

Groups were compared regarding age, age of onset of symptoms, age at diagnosis, and the time elapsed to diagnosis, using one-way analysis of variance and the multiple comparison procedures of the Student-Newman-Keuls method. The χ^2 -test was performed to eval-

uate differences between groups in terms of specific IgE positivity. The level of significance was set at $p < 0.05$.

RESULTS

This study included 72 CVID patients. The mean age was 38.2 years, and 37 of the 72 (51.4%) were women. Age of onset of symptoms, age at diagnosis, and the delay in establishing the diagnosis of CVID are shown in Table 1.

CVID patients were classified according to the presence or absence of rhinitis. Chronic rhinitis was observed in 59 CVID patients (81.9%), and 13 patients (18.1%) had no history of rhinitis. Thirty-one of 59 patients (52.5%) with chronic rhinitis presented a clinical history consistent with AR and 28 patients (47.5%) presented a history suggestive of NAR. In the group of patients without chronic rhinitis there was a higher prevalence of men (69.2%) and in the group suggestive of AR, women (61.3%) were more numerous, as shown in Table 2. A history suggestive of asthma was present in 29 patients (40.3%), of which 26 (89.7%) also had a history of chronic rhinitis.

Patients with a history suggestive of AR or NAR presented an earlier age of onset of CVID symptoms ($p < 0.001$ and $p = 0.008$, respectively) than did those without rhinitis. Moreover, patients with probable AR were diagnosed with CVID earlier than those of the other groups ($p = 0.019$). These data are given in Fig. 1. However, there was no statistical difference ($p = 0.799$) in the time elapsed to the diagnosis of CVID among the three groups.

When the chronological characteristics of patients with CVID were analyzed according to absence or presence of rhinitis and gender, we observed that the age at diagnosis and the time elapsed to diagnosis were higher in women without rhinitis than in the others ($p < 0.0001$ and $p < 0.0201$, respectively), as shown in Table 2.

Total IgE was undetectable in most patients (86.1%).

All patients were tested for specific IgE to aeroallergens. The skin-prick test was positive in only 3 (of 70) CVID patients, and serum-specific IgE was positive in only 2 patients (of the 61 tested). One patient was positive for specific IgE both *in vivo* and *in vitro* (Table 3) and, unfortunately, two patients with positive skin-prick test were not submitted to *in vitro* testing.

Thus, the presence of specific IgE to aeroallergens was shown in only 4 (5.6%) of 72 patients with CVID, all belonging to the group suggestive of AR. In this group, the frequency of positive specific IgE was 12.5% ($p = 0.037$), as shown in Fig. 2. The tests were positive for *D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *A. fumigatus* and *C. familiaris*.

As initial manifestations suggestive of CVID, recurrent pneumonia was observed in 73.6% of patients, recurrent sinusitis in 62.5%, and recurrent or chronic diarrhea in 40.3% of them. An interesting observation is that of the 72 patients, 6 (8.3%) had evolved from IgA deficiency (IgAD) into CVID.

Recurrent or chronic rhinosinusitis was present before the diagnosis of CVID in 20 patients (64.5%), with suggestive AR in 17 patients (60.7%) with NAR, and in 8 patients (61.5%) in the group without rhinitis ($p > 0.05$).

Table 2 Chronologic characteristics of patients with CVID, with (suggestive of allergic or nonallergic) or without rhinitis, according to gender

Chronologic Characteristics	Suggestive AR		Suggestive NAR		No Chronic Rhinitis	
	Male (n = 12)	Female (n = 19)	Male (n = 14)	Female (n = 14)	Male (n = 9)	Female (n = 4)
Mean age at study onset (yr)	33.3	35.1	43.5	38.1	33.1	60.0
Mean age at onset of symptoms (yr)	9.0	10.1	17.3	11.1	20.3	29.3
Mean age at diagnosis (yr)	22.7	26.2	31.8	27.2	27.3*	55.0*
Mean time to diagnosis (yr)	13.7	16.2	14.5	16.1	7.0#	25.8#

Patients (n) = 72.
Statistical analysis: *p = 0.0001; #p = 0.0201; Student's t-test.
AR = allergic rhinitis; NAR = nonallergic rhinitis; CVID = common variable immunodeficiency.

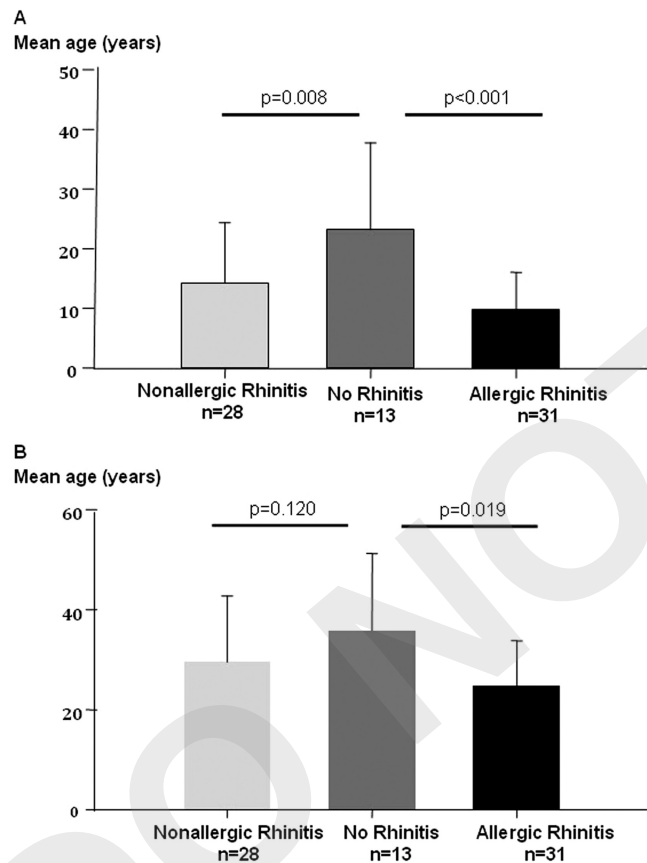


Figure 1. Chronologic characteristics of patients with common variable immunodeficiency, according to the presence or absence of rhinitis (suggestive allergic or nonallergic). (A) Age at onset of symptoms of common variable immunodeficiency (CVID); (B) Age at diagnosis of CVID. Statistical analysis: Student-Newman-Keuls method.

DISCUSSION

Chronic rhinitis is a common manifestation in CVID patients.⁷ In the present study, 59 of 72 CVID patients (81.9%) had chronic rhinitis, suggestive of AR or NAR.

The etiology of chronic rhinitis may be allergic in CVID patients, because many had personal and family histories strongly suggestive of atopy. In this study, allergy was only confirmed by the detection of specific IgE aeroallergens in four patients (5.6%) and all of them belonged to the group with suggestive AR.

Although the skin-prick test possesses greater sensitivity than serum-specific IgE,²⁸ in this study one patient was found to have positive specific IgE only in the *in vitro* test. Perhaps this was caused

Table 3 Specific IgE in patients with CVID, according to the presence or absence of rhinitis (suggestive of allergic or nonallergic)

Presence or Absence of Rhinitis	Skin-Prick Test		Serum-Specific IgE	
	Positive	Negative	Positive	Negative
Suggestive AR (n = 31)	3	27	2	26
Suggestive NAR (n = 28)	0	28	0	26
No chronic rhinitis (n = 13)	0	12	0	7

Patients (n) = 72.
One patient was positive for specific IgE *in vivo* and *in vitro*.
Statistical analysis: *p = 0.037; χ^2 .
AR = allergic rhinitis; NAR = suggestive nonallergic rhinitis; CVID = common variable immunodeficiency.

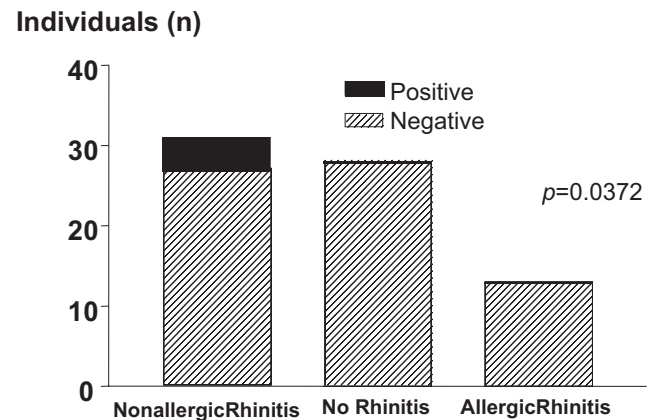


Figure 2. Specific IgE (skin-prick test and/or serum-specific IgE) in common variable immunodeficiency (CVID) patients, according to presence or absence of rhinitis (suggestive allergic or nonallergic). Patients (n): nonallergic rhinitis = 28, no rhinitis = 13, and allergic rhinitis = 31. Statistical analysis: χ^2 -method.

by a variation that may occur in CVID patients. These patients barely have detectable total serum IgE and specific IgE to aeroallergens.^{9,20} In this study, AR diagnosis by conventional tests was occasional, although 43.1% of participants had a history and symptoms highly suggestive of atopy.

Additional tests may be necessary to confirm the allergic etiology of the rhinitis observed in some of these CVID patients. One suggestion would be the nasal provocation test using prevalent allergens. In a previous study, CVID patients with a suggestive

history of allergic asthma in the absence of specific IgE were assessed by conventional tests. We showed that 4 of 15 patients (26.7%) presented a positive response to bronchial provocation tests with *D. pteronyssinus*.²⁰

In this study, patients' ages were similar in the three groups (history suggestive of AR, NAR, and absent chronic rhinitis). It was observed that the time elapsed for CVID diagnosis was longer than that reported in the literature,^{1,5,29} with an average time of 14.8 years, regardless of the presence or absence of chronic rhinitis.

The excessive average time between onset of symptoms and CVID diagnosis observed in this study may be caused by the fact that the latter is a rare disease and most patients are seen only in emergency care services and/or assisted by several doctors during their clinical evolution. Often this delay is caused by the difficulty encountered in establishing laboratory diagnosis, given the broad clinical presentation of CVID. A previous study in this country showed a lapse in the time necessary for the diagnosis of CVID of 10 years.⁴

In this study, patients with chronic AR or NAR were, on average, younger at the onset of the appearance of their immunodeficiency symptoms than those without rhinitis; however, the diagnosis of CVID was established earlier only in the group suggestive of AR.

It is possible that some of the patients with a history of probable AR may have progressed from IgAD to CVID, because the prevalence of atopy is much higher in patients with IgAD. If IgAD evolves into CVID, a difficulty in diagnosing IgE-mediated allergic diseases may be encountered, because the production of immunoglobulin in greater amounts is probably impaired.^{30,31}

Although the age at the onset of symptoms was similar in all groups (with or without chronic rhinitis), the time taken to diagnose CVID in women without rhinitis was longer, suggesting that in this group of patients (CVID and without rhinitis), the presence of rhinosinusitis would constitute a warning sign regarding the suspicion and diagnosis of this disease (Table 2).

Despite the appropriate i.v. gammaglobulin replacement therapy, most patients (90.3%) had chronic or recurrent infectious rhinosinusitis, which is consistent with the reports found in the literature.^{18,19}

Total serum IgE levels were undetectable in most patients (86.1%) in this study. Popa and colleagues⁹ observed that total serum IgE in patients with IgG deficiency and chronic obstructive pulmonary diseases was lower than that found in patients with the same respiratory disease but without hypogammaglobulinemia.

One probable explanation for the lower prevalence of serum allergen-specific IgE in CVID patients with probable AR is their impaired capacity to produce immunoglobulin on a larger scale while there is still local specific IgE production to aeroallergens. Several authors have shown the local production of IgE in patients with rhinitis or asthma, by detecting the transcription and mRNA expression of IgE in the local mucosa.³²⁻³⁴

The hypothesis that chronic rhinitis could mask and extend the time lapse to CVID diagnosis was not confirmed by this study. Consequently, it is possible that rhinosinusitis or other upper airway symptoms are not as important for CVID diagnosis as are other infections such as pneumonia and chronic diarrhea.

Another important point in evaluating patients with CVID is the high frequency of chronic rhinitis. Twenty-eight patients (38.9%) presented NAR and it is likely that in these cases the probable cause is a postinfectious complication, because infectious rhinosinusitis is a very prevalent manifestation in CVID patients.^{8,9}

In this study, most patients (26 of 29) with a history of asthma belonged to the groups with chronic rhinitis. Several studies on the influence of rhinitis on asthma have observed a close association between the presence of persistent rhinitis and asthma in atopic or nonatopic patients.³⁵⁻³⁷

In conclusion, the identification of AR in CVID patients through detection of specific IgE (*in vivo* or *in vitro*) was poor because only 5.6% of patients had measurable specific IgE. However, among the 43.1% of patients who presented a history suggestive of AR, 12.5% had positive specific IgE tests, reinforcing the aforementioned hypothesis. Moreover, the presence of chronic rhinitis in CVID patients (whether probably allergic or nonallergic) was associated with an earlier age of onset of the immunodeficiency symptoms.

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