

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

ASBAI – Associação Brasileira
de Alergia e Imunologia

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Importance of IgE in chronic spontaneous urticaria

Importância da IgE na urticária crônica espontânea

Rosana Câmara Agondi¹

Chronic urticaria (CU) is a common, heterogeneous disease often associated with significant impairment of quality of life. CU is classified into spontaneous (CSU) or inducible (CIU) based on the absence or presence of a specific trigger, respectively. Mast cells have a central role in the pathogenesis of CU, as several studies have shown an increase in histamine or in the number of mast cells in skin biopsies of patients with CU. This is also attributed to the good response to antihistamines.¹ Although mast cells express a variety of membrane receptors, mast cell activation in CSU is mainly mediated by immunoglobulin E (IgE) and its high-affinity receptor, FcεRI. The importance attributed to IgE and its receptor arises from significant advances in the treatment of CU in the last decade, with the introduction of omalizumab, a monoclonal anti-IgE antibody. Seventy to 80% of patients with CSU refractory to antihistamines (after a fourfold increase in the dose) achieve complete disease control with omalizumab.^{2,3}

However, how mast cells are activated in CSU remains unknown. The main hypothesis is that activation occurs through autoimmune mechanisms: (a) the development of IgG anti-IgE autoantibodies; and (b) the development of IgE antibodies to autoantigens, such as thyroid peroxidase.

Therefore, these mechanisms could explain why patients with CSU have a good response to omalizumab. However, the response to omalizumab can vary, with some showing an early response after the first dose, others responding between the second and sixth doses, and a small portion may not respond adequately to omalizumab.⁴

Several retrospective and prospective studies have evaluated biomarkers that could predict the severity of CSU and the early or late response to omalizumab. In this edition of Arquivos de Asma, Alergia e Imunologia (AAAI), Girardello et al.⁵ described the response to omalizumab in a group of patients with severe CSU, while Bastos Jr et al.⁶ conducted a detailed retrospective study including potential biomarkers to assess disease severity and treatment response.

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Asthma in adolescents: what did ERICA study show us?

Asma em adolescentes: o que o estudo ERICA nos mostrou?

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ABSTRACT

Asthma is a heterogeneous disease characterized by a history of respiratory symptoms that vary in intensity and over time. Due to its high prevalence, asthma is considered a global public health problem affecting all age groups, especially children and adolescents. This study aimed to analyze scientific papers on asthma based on the Study of Cardiovascular Risks in Adolescents (ERICA). We provide a narrative review of original articles on asthma based on ERICA data published in indexed journals in English and Portuguese. ERICA was a national multicenter study conducted in 2013 and 2014 that investigated the prevalence of asthma and cardiovascular risk factors, including obesity, diabetes mellitus, systemic arterial hypertension, dyslipidemia, smoking, sedentary lifestyle, and inadequate eating habits, and the association between these factors in adolescents aged 12 to 17 years, students from public and private schools in Brazilian cities of more than 100,000 population. In the 5 selected studies, the prevalence of asthma was significantly higher in female adolescents in all capitals and macro-regions of Brazil, occurring predominantly in the southeast region of the country. In addition, asthma was strongly associated with smoking (passive and active) as well as with short sleep duration, but not with serum vitamin D levels. Regarding metabolic parameters, metabolic syndrome and some of its components, such as waist circumference, were significantly associated with severe asthma in Brazilian adolescents.

Keywords: Asthma, adolescent, smoking, metabolic syndrome, sleep.

RESUMO

A asma é uma doença heterogênea caracterizada pela história de sintomas respiratórios que variam de intensidade e ao longo do tempo. Devido à sua alta prevalência, constitui um problema mundial de saúde pública, atingindo todas as faixas etárias, em especial crianças e adolescentes. O objetivo deste artigo foi analisar as produções científicas sobre asma baseadas no Estudo de Riscos Cardiovasculares em Adolescentes (ERICA). Trata-se de uma revisão narrativa incluindo os artigos originais sobre asma baseados nos dados do ERICA, publicados em periódicos indexados em inglês e português. O ERICA foi um estudo multicêntrico nacional realizado em 2013 e 2014, que investigou a prevalência de asma e fatores de risco cardiovascular, incluindo obesidade, *diabetes mellitus*, hipertensão arterial sistêmica, dislipidemia, tabagismo, sedentarismo, hábitos alimentares inadequados, e a associação entre esses fatores, em adolescentes de 12 a 17 anos, estudantes de escolas públicas e privadas de municípios brasileiros com mais de 100.000 habitantes. Nos cinco estudos selecionados, foi possível demonstrar que a prevalência de asma foi significativamente maior entre adolescentes do sexo feminino em todas as capitais e macrorregiões do Brasil, com predomínio da doença na região Sudeste do nosso país. Além disso, a asma esteve fortemente associada ao tabagismo (passivo e ativo) e foi associada à duração curta do sono. Por outro lado, não esteve associada com os níveis séricos de vitamina D. Em relação aos parâmetros metabólicos, foi observado que a síndrome metabólica e alguns de seus componentes, como a circunferência abdominal, estiveram significativamente associados à asma grave em adolescentes brasileiros.

Descritores: Asma, adolescente, tabagismo, síndrome metabólica, sono.

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Introduction

Asthma is a heterogeneous disease characterized by a history of respiratory symptoms that vary in intensity and over time.¹ Variable obstruction of pulmonary airflow occurs, which can become persistent.¹ It is usually associated with bronchial hyperresponsiveness and airway inflammation.¹

Due to its high prevalence, asthma is considered a global public health problem affecting all age groups, especially children and adolescents.² It is a complex disease with several potential determinants, from genetic to environmental factors, including lifestyle.³ Epidemiological studies have shown that smoking, air pollution, urban lifestyle, obesity, fast food, and low antioxidant content are associated with asthma in children and adolescents.³

Furthermore, in low- and middle-income countries such as Brazil, people with asthma have a disproportionately high morbidity and mortality rate, suggesting that socioeconomic factors may influence these rates, either due to overall poorer living conditions or limited access to treatment.⁴

The Study of Cardiovascular Risks in Adolescents (ERICA, for the acronym in Portuguese) was a national multicenter study that aimed to estimate the prevalence of cardiovascular risk factors, including obesity, diabetes mellitus, systemic arterial hypertension, dyslipidemia, passive and active smoking, sedentary lifestyle, inadequate eating habits, and the association between these factors in adolescents aged 12 to 17 years, students from public and private schools in Brazilian cities of more than 100,000 population.⁵ In this survey, conducted in 2013 and 2014, adolescents also answered a standardized written asthma questionnaire from the International Study of Asthma and Allergies in Childhood (ISAAC) to estimate the prevalence of asthma in this population.^{6,7}

Several studies have been based on ERICA data, studying the prevalence of asthma and possible associated factors in Brazilian adolescents.⁸⁻¹² The aim of this article was to analyze published studies on asthma based on ERICA results.

Methods

This is a narrative review of original articles on asthma based on ERICA data published in indexed journals in English and Portuguese. The MEDLINE (National Center for Biotechnology Information, Bethesda, MD) and LILACS (Latin American and

Caribbean Health Science Literature Database) databases were searched using the following keywords: “asthma” AND “adolescent” OR “adolescence” AND “ERICA,” from 2016 (when the first ERICA article on asthma was published) to the present day. We added 1 article that was not found through this search, despite being within the inclusion criteria.

The ISAAC standardized written asthma module questionnaire for the age group 13 to 14 years, validated and translated into Portuguese, was used for the diagnosis and classification of asthma severity in ERICA. The presence of active asthma was obtained as the percentage of positive answers to the question “Have you had wheezing in the last 12 months?”.^{6,7} Adolescents with ≥ 4 wheezing attacks in the last 12 months were considered to have severe asthma.¹³ The presence of asthma diagnosed by a doctor was defined as the percentage of positive answers to the question: “Has a doctor told you that you have asthma?”.^{6,7}

Results

We included 5 studies on adolescent asthma based on ERICA data. Their main findings are described below.

ERICA: prevalence of asthma in Brazilian adolescents (2016)

This article aimed to describe the prevalence of active asthma and medical diagnosis of asthma in Brazilian adolescents.⁸ Data from 74,589 adolescents participating in ERICA were used. The overall prevalence of active asthma was 13.1%, significantly higher in female (14.8%; 95% CI 13.7-16.0) than in male (11.2%; 95% CI 10.3-12.2) adolescents, and among students from private schools (15.9%; 95% CI 14.2-17.7) than public schools (12.4%; 95% CI 11.4-13.4). The overall prevalence of a medical diagnosis of asthma was 8.7% (95% CI 8.2-9.1), with no significant differences between sex, age group, or skin color.⁸ Table 1 shows the prevalence of active asthma in macro-regions and in public and private schools.

The geographical distribution of the prevalence of active asthma in the country was highest in the Southeast (14.5%; 95% CI 12.9-16.1) and in São Paulo (16.7%; 95% CI 14.7-18.7), Belo Horizonte (15.8%; 95% CI 13.9-17.7), and Goiânia (15.4%; 95% CI 13.1-17.7). The North region had the lowest prevalence among the macro-regions (9.7%; 95% CI 9.7-10.5), as well as Teresina (6.3%; 95% CI 4.9-7.7),

São Luís (7.4%; 95% CI 6.0-8.8), and João Pessoa (7.8%; 95% CI 6.4-9.2). The prevalence of active asthma was higher among female adolescents in all Brazilian capitals and regions. As for the medical diagnosis of asthma, the highest prevalence was found in the North (13.5%; 95% CI 12.7-14.2) and in Porto Alegre (19.8%; 95% CI 17.5-22.3), Belém (15.7%; 95% CI 13.5-17.8), and Vitória (15.5%; 95% CI 12.6-18.3). On the other hand, the Midwest region had the lowest prevalence among the macro-regions (6.9%; 95% CI 6.0-7.8), as well as Cuiabá (4.8%; 95% CI 3.8-5.9), Campo Grande (5.4%; 95% CI 4.2-6.6), and João Pessoa (6.5%; 95% CI 5.2-7.7).⁸

Severe asthma is associated with metabolic syndrome in Brazilian adolescents (2018)

This study aimed to evaluate the association between asthma and metabolic alterations in Brazilian adolescents participating in the ERICA study.⁹ A total of 37,410 participants were included and completed the questionnaire, biochemical determinations, anthropometric, and blood pressure measurements. The definition of metabolic syndrome (MS) considered increased waist circumference (WC) and the presence of 2 or more risk factors: high triglycerides ≥ 150 mg/dL and/or high blood glucose ≥ 100 mg/dL and/or reduced HDL-cholesterol

Table 1

Prevalence (%) of asthma and physician-diagnosed asthma among Brazilian adolescents. ERICA, 2013-2014

Variable	Sample	Active asthma		Physician-diagnosed asthma	
		%	95% CI	%	95% CI
Macro-regions					
North	15073	9.7	9.0-10.5	13.5	12.7-14.2
Northeast	23167	10.1	8.8-11.4	9.0	8.1-9.9
Midwest	9727	13.6	11.9-15.3	6.9	6.0-7.8
Southeast	17080	14.5	12.9-16.1	7.6	6.8-8.3
South	9542	13.9	12.5-15.3	10.4	8.9-11.9
Sex					
Women	41225	14.8	13.7-16.0	8.5	7.8-9.1
Men	33364	11.2	10.3-12.2	8.9	8.2-9.5
Age (years)					
12-14	34141	12.6	11.3-13.9	8.9	8.3-9.5
15-17	40448	13.4	12.3-14.6	8.4	7.7-9.1
Types of school					
Private	15882	15.9	14.2-17.7	9.6	8.7-10.5
Public	58707	12.4	11.4-13.4	8.5	7.9-9.0
Brazil	74589	13.1	12.1-13.9	8.7	8.2-9.1

95% CI = 95% confidence interval.

Adapted from Kuschnir FC, et al.⁸.

< 40 mg/dL or < 50 mg/dL in young girls aged 16-17 years old and/or high blood pressure $\geq$ 130/85 mm Hg.⁹ The prevalence of active asthma and severe asthma were 13.8% (95% CI 12.4-15.2) and 2.09% (95% CI 1.95-2.24), respectively. The prevalence of MS was 2.3% (95% CI 2.14-2.45). Active asthma was associated with high WC (prevalence ratio - PR 1.19; 95% CI 1.00-1.43) and high LDL-cholesterol (PR 1.28; 95% CI 1.08-1.48), but not MS (PR 0.94; 95% CI 0.67-1.13) in this sample. On the other hand, severe asthma was associated with MS (PR 2.43; 95% CI 1.39-4.27), and this association remained significant after adjusting for age, sex, active smoking, and body mass index (BMI) - (PR 1.71; 95% CI 1.03-2.82). In addition, significant associations were observed between severe asthma and obesity (PR 1.28; 95% CI 1.02-1.62), high WC (PR 1.74; 95% CI 1.16-2.61), hyperglycemia (PR 1.78; 95% CI 1.05-2.98), and hyperinsulinemia (PR 1.55; 95% CI 1.03-2.33), which are known components of MS.⁹

ERICA: smoking is associated with more severe asthma in Brazilian adolescents (2019)

This study investigated the association between smoking and asthma.¹⁰ A total of 66,394 ERICA participants were included with complete questionnaires on asthma, smoking, lifestyle, and social and demographic variables. The variables relating to smoking were defined as “experimentation” (adolescents who had tried cigarettes at least once in their lives); “current smoking” (those who had smoked cigarettes for at least 1 day in the last 30 days); “frequent smoking” (having smoked cigarettes for at least 7 days in a row in the last 30 days), and “passive smoking” (participants whose household had at least 1 smoker).¹⁰

The prevalence of active asthma and severe asthma were 13.2% (95% CI: 12.9-13.5) and 2.4% (95% CI: 2.3-2.5), respectively. The prevalence of active asthma was significantly higher among female students, of white/other skin color and from private schools. As for smoking, 18.2% (95% CI: 17.3-19.1) of adolescents had tried cigarettes. Of these, 25.3% were classified as “current smokers” and 11.8% as “frequent smokers.” The prevalence of adolescents with at least 1 household smoker was 27.5% (95% CI: 26.6-28.3). The prevalence of active asthma and severe asthma was significantly higher in adolescents exposed to: experimentation (active asthma: PR 1.78; 95% CI 1.51-2.09; severe asthma: PR 2.01; 95% CI

1.35-2.98); active smoking (active asthma: PR 2.08; 95% CI 1.65-2.64; severe asthma: PR 2.29; 95% CI 1.38-3.82); frequent smoking (active asthma: PR 2.25; 95% CI 1.64-3.07; severe asthma: PR 2.41; 95% CI 1.23-4.73); and passive smoking (active asthma: PR 1.47; 95% CI 1.27-1.67; severe asthma: PR 1.66; 95% CI 1.19-2.32). These associations remained significant after adjustments.¹⁰ In addition, a dose-response relationship was observed: the higher the number of smokers in the household, the higher the prevalence of asthma, as shown in Figure 1.¹⁰

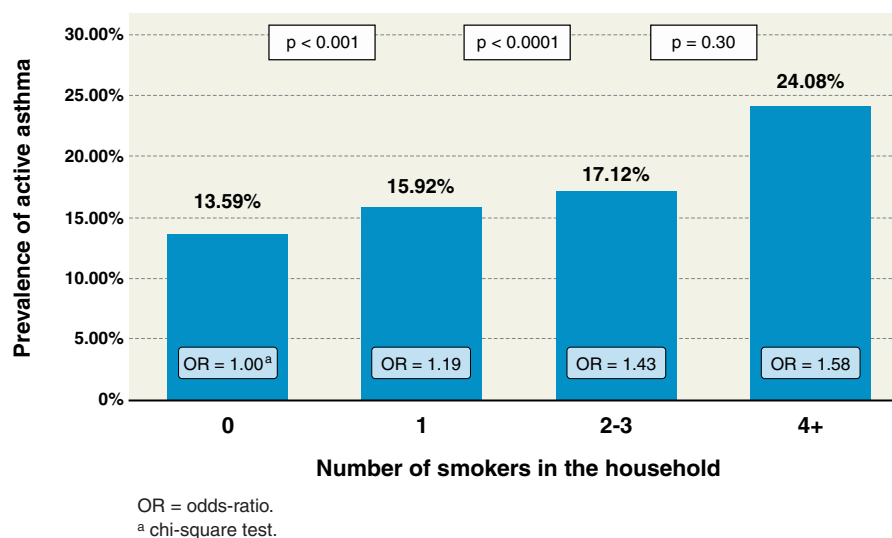
Association between asthma and sleep hours in Brazilian adolescents: ERICA (2021)

This study aimed to investigate the association between asthma and bedtime in adolescents participating in ERICA.¹¹ Short sleep duration (SSD) was considered as sleeping < 7 hours per night, which has already been used in other national studies. The prevalence of common mental disorders (CMD), which correspond to non-psychotic mental disorders, primarily associated with symptoms of depression, anxiety, and nonspecific and somatic complaints, was also assessed as a possible confounding factor in the asthma-sleep association, using the General Health Questionnaire, 12-item version (GHQ-12), validated for the Brazilian population. Those with a score $\geq$ 3 were classified as CMD cases.¹¹

A total of 59,442 participants with complete data were included. The prevalence of active asthma was significantly higher in students with SSD (PR: 1.17; 95% CI: 1.01-1.35; $p = 0.034$). On the other hand, there was no association between active asthma and age group. The association between asthma and SSD remained significant even after adjusting for sex, age group, type of school, weight status, and CMD.¹¹

Asthma and vitamin D in Brazilian adolescents: Study of Cardiovascular Risks in Adolescents (ERICA) (2021)

This study aimed to analyze the association between asthma and serum vitamin D levels in Brazilian adolescents.¹² Serum concentrations of 25-hydroxyvitamin D were dichotomized into: sufficient levels ($\geq$ 20 ng/mL) or insufficient/deficient levels (< 20 ng/mL). A total of 1,053 adolescents from 4 Brazilian state capitals (Fortaleza, Brasília, Rio de Janeiro, and Porto Alegre) were assessed. The prevalence of active asthma was 15.4%, and vitamin insufficiency/

**Figure 1**

Association between the number of smokers in the household and the prevalence of active asthma in Brazilian adolescents. ERICA, 2013-2014

Adapted from Jordão EAOC et al, 2019.¹⁰

deficiency was 21%. There was no statistically significant association between active asthma and hypovitaminosis D. The prevalence of active asthma and hypovitaminosis D were, respectively, 2.34 (95% CI 1.28-4.30) and 3.22 (95% CI 1.75-5.95) times higher in Porto Alegre than in Rio de Janeiro, regardless of possible confounding factors. However, there were no significant associations between the prevalence of active asthma and variables related to vitamin D in any of the cities studied.¹²

Discussion

Studies on asthma using ERICA data have shown that the prevalence of asthma was significantly higher among female adolescents in all Brazilian capitals and macro-regions, with a predominance of the disease in Southeastern Brazil.⁸ Furthermore, asthma was strongly associated with smoking (passive and active)¹⁰ and short sleep duration.¹¹ On the other hand, it was not associated with serum vitamin D levels.¹² In relation to metabolic parameters, it was observed that MS and some of its components, such as WC, were significantly associated with severe asthma in Brazilian adolescents.⁹

ISAAC was one of the key global studies designed to investigate the epidemiology of asthma in children and adolescents. It is a multicenter study that evaluated the prevalence of asthma, allergic rhinoconjunctivitis, and atopic eczema in children (6 to 7 years old) and adolescents (13 to 14 years old).⁶ The first phase of ISAAC was completed in 1996 and involved around 450,000 adolescents from 155 centers located in 56 countries.¹⁴ The global prevalence of asthma in adolescents, defined as the presence of wheezing in the last 12 months, was 13.2%. In Brazil, the prevalence was 19.5%.¹⁴ ISAAC phase III was conducted 7 years after phase I and involved almost 1 million adolescents from 233 centers in 97 countries.^{15,16} The global prevalence of asthma increased to 13.7%. In Brazil, the prevalence of active asthma in ISAAC phase III was 19%, ranging from 11.8%-30.5%.^{15,16}

The Brazil's National Survey of School Health (*Pesquisa Nacional em Saúde do Escolar - PeNSE*), another cross-sectional study conducted nationwide in 2012, involved 109,104 Brazilian adolescents, 9th grade students from public and private schools, the majority (86%) aged between 13 to 15 years.¹⁷ The self-report ISAAC questionnaire was used to estimate

the prevalence of asthma, and found rates of 23.2% and 12.4% for asthma symptoms and physician-diagnosed asthma, respectively.¹⁷ When compared to the results found by ISAAC in 5 Brazilian state capitals, the prevalence of asthma increased in São Paulo, Curitiba, and Porto Alegre, whereas it decreased in Salvador.¹⁷

When comparing ERICA with other studies based on the ISAAC questionnaire in different locations in Brazil, ERICA showed lower prevalence rates for active asthma and physician-diagnosed asthma.^{8,17,18} The 2012 PeNSE showed rates of 23.2% and 12.4%, respectively, for active asthma and physician-diagnosed asthma in adolescents aged 13 to 15 years.¹⁷ Similarly to our results, the highest percentages of active asthma (24.9% vs 14.5%) were observed in the Southeast region and of physician-diagnosed asthma (18.4% vs 13.5%) in the North region. Another similar result was the higher prevalence of active asthma in girls compared to boys.¹⁷ Solé et al. assessed the prevalence of asthma in adolescents aged 13 to 14 in 7 Brazilian cities participating in the ISAAC phase III in 2003 and its temporal trend after 9 years of study.¹⁸ The mean prevalence of active asthma decreased over this period (19.5% vs 17.5%), and the prevalence of physician-diagnosed asthma increased (14.3% vs 17.6%), both rates higher than those found in ERICA.¹⁸ The prevalence of physician-diagnosed asthma found in ERICA was also lower when compared to the ISAAC and PeNSE results.^{8,17,18}

As for the prevalence of active asthma among students from public and private schools, PeNSE¹⁷ found no significant differences. ERICA found a higher percentage of active asthma among adolescents from private schools.⁸ This result can be explained since adolescents from private schools are more likely to have better family financial conditions and consequently greater access to health services.⁸

Regarding the association between asthma, MS and its components, active asthma was associated with high WC and high LDL-cholesterol, but ERICA found no association with MS.⁹ On the other hand, severe asthma was associated with MS and several of its components (obesity, high WC, hyperglycemia, and hyperinsulinemia).⁹ Most of the epidemiological data published worldwide on the relationship between asthma and MS and/or its components come from studies conducted in adults.^{19,20} A Spanish study with 85,555 workers showed that high WC or BMI, high triglycerides or low HDL-cholesterol were

significantly associated with wheezing.¹⁹ Another study with 121,965 Parisian adults showed an association between altered lung function and MS, and the best predictor of this outcome was obesity, with similar results both in men and women.²⁰ In the adolescent population, Forno et al. observed in a sample with 1,429 Americans that insulin resistance was associated with changes in lung function (reduced values of forced expiratory volume in the first second [FEV₁] and forced vital capacity [FVC]), and MS was associated with a lower FEV₁/FVC ratio.²¹ ERICA did not analyze lung function, although stronger and more significant associations were found between the components of MS and severe asthma, compared to active asthma.⁹ Thus, the relationship between asthma and MS may vary according to asthma severity, and this association may be reflected in altered lung function in adolescents with abnormalities in glucose and lipid metabolism.

In a longitudinal study evaluating 2 German cohorts (GINIplus and LISAPlus), researchers investigated early life events, as well as environmental and lifestyle factors, and correlated them with lung function in adolescents at the age of 15.²² It was observed that lung infections in early life were early events associated with airflow limitation and FEF₂₅₋₇₅ (intermediate forced expiratory flow, between 25 and 75%). The environmental factors associated with lung function at the age of 15 were: passive smoking, vitamin D concentration, BMI, and asthma diagnosis.²² Although ERICA did not assess lung function and it was a cross-sectional study, we observed more significant associations between severe asthma and smoking, compared to active asthma.¹⁰ Similarly, we found stronger associations between metabolic alterations, such as increased BMI and severe asthma.⁹ On the other hand, we found no significant associations between active or severe asthma and hypovitaminosis D.¹²

PeNSE assessed aspects other than prevalence related to asthma in Brazilian adolescents. One study looked at socioeconomic, environmental, psychosocial, family-related and lifestyle factors associated with asthma in Brazilian adolescents.²³ Data from 109,104 PeNSE participants was evaluated and found that exposure to violence (feeling unsafe at school, bullying, exposure to firearms) and physical aggression perpetrated by an adult in the family were environmental factors most strongly associated with asthma.²³ As for mental health indicators, feelings of loneliness and sleeping problems were the most

significant factors.²³ Among behavioral factors, the strongest association was with smoking.²³ ERICA also found associations between asthma and short sleep duration¹¹ and, more significantly, with smoking.¹⁰ However, no data were collected on violence, so no further studies could be conducted on this subject.

Another study based on PeNSE data assessed asthma-related factors in adolescents²⁴ and analyzed data from 106,983 participants. The prevalence of asthma was 23.2% and factors were found to be independently associated with asthma.²⁴ These include: women (OR=1.17); age < 14 years (OR=1.17); more days consuming ultra-processed foods (OR=1.16); active smoking (OR=1.36); alcohol consumption (OR=1.37); use of illicit drugs (OR=1.37); and having sought health care in the last year (OR=1.67).²⁴ Similarly, ERICA found an association with women⁸ and active smoking.¹⁰ No analysis was conducted on the consumption of ultra-processed foods and alcoholic beverages, but these data have already been collected and could be evaluated in future studies.

This article has limitations, including the fact that it is a review based on secondary data from only a few studies. In addition, ERICA was a cross-sectional study and no causal relationships could be established between the factors assessed and asthma. On the other hand, ERICA was a nationwide multicenter study with a representative sample of Brazilian adolescents using the ISAAC questionnaire, standardized worldwide and validated for our context. It was therefore possible to build up an extensive overview on asthma and some of its determinants.

In conclusion, asthma is still a very prevalent disease in the Brazilian adolescent population and is an important public health problem in this age group. It is multifactorial in nature and is associated with various factors such as smoking, metabolic alterations, and sleep disorders. The study of different environmental and lifestyle factors associated with asthma could broaden our understanding of the disease and, consequently, improve its control and management.

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Biomarkers of chronic urticaria: what are their role?

Biomarcadores na urticária crônica: qual o seu papel?

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ABSTRACT

Urticaria is a disease of global importance that can be debilitating for most patients. It is characterized by episodes of wheals, angioedema, or both, determined by the activation of mast cells and other inflammatory cells with the release of several mediators. The etiology is complex, involving specific phenotypes and therapies. Chronic urticaria has a recurrent and unpredictable course that can last for years. The prevalence is typically higher in females, with a peak incidence between 20 and 40 years of age. The disease can be classified by severity, impact on quality of life, and therapeutic response. A biomarker is a measurable clinical or laboratory characteristic of a biological state or condition that can influence or predict the incidence of outcome or disease. This study provides a review of the main biomarkers considered promising and with the best evidence related to duration, disease activity, and therapeutic response.

Keywords: Chronic urticaria, angioedema, biomarkers, autoimmunity.

RESUMO

A urticária é uma doença com comprometimento universal, e debilitante para a maioria dos pacientes. Caracteriza-se pela ocorrência de episódios de urticas, angioedema ou ambos, determinados pela ativação de mastócitos e outras células inflamatórias com a liberação de vários mediadores. Apresenta etiologia complexa com fenótipos e terapias bem específicas. A urticária crônica possui evolução recorrente e imprevisível, podendo estender-se por anos. Caracteristicamente possui maior prevalência no sexo feminino, com pico de ocorrência entre 20 e 40 anos. A doença pode ser diferenciada pela gravidade, impacto na qualidade de vida do paciente e resposta terapêutica. Biomarcador é uma característica clínica ou laboratorial mensurável de algum estado ou condição biológica, o qual pode influenciar ou prever a incidência de desfecho ou doença. O objetivo deste artigo é realizar uma revisão dos principais biomarcadores promissores e com melhor evidência relacionados à duração, atividade da doença e resposta terapêutica.

Descritores: Urticária crônica, angioedema, biomarcadores, autoimunidade.

Introduction

Chronic urticaria (CU) is a common skin disease with a negative impact on several aspects of patients' lives. CU is characterized by the occurrence of wheals and/or angioedema for a period of 6 weeks or longer. It can be classified as chronic spontaneous urticaria (CSU), when there is no specific trigger, or chronic

inducible urticaria (CIndU), in which symptoms are induced by specific triggers.^{1,2}

The lesions result from activation of mast cells and other inflammatory cells, such as basophils and eosinophils, and the subsequent release of their mediators.³ CU has a recurrent and unpredictable

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course that can last for years, with about 20% of patients remaining symptomatic after 5 years. The prevalence is typically higher in females, with a peak incidence between 20 and 40 years of age. The disease can be classified by severity, impact on quality of life, and clinical outcome.^{1,3}

Over the last decade, numerous studies have been conducted in an attempt to elucidate the mechanisms involved in the development of CU and to identify potential biomarkers.⁴ A biomarker is a measurable clinical or laboratory characteristic of a biological state or condition that allows us to know, for example, the state of a disease or the response to a drug.⁵

The main difficulty in establishing biomarkers of CU lies in the heterogeneity of the clinical presentation and its complex pathogenesis. There are multiple ways of mast cell activation, with the participation of numerous cells and molecules, leading to different endotypes and phenotypes. A better understanding of these endotypes, through biomarkers, will help better understand the course of CU and find targets for new therapies.⁶

This study aimed to review the main biomarkers considered promising and with the best evidence related to disease activity, therapeutic response, and natural course of CU.

Methods

We conducted a search in Science Direct, PubMed, and Latin American and Caribbean Health Sciences Literature (LILACS) databases for original articles, reviews, guidelines, and consensus statements published in the past 20 years by using the following search terms: chronic urticaria, biomarkers, duration, prediction, prognosis, and treatment.

Biomarkers

In CU, biomarkers are useful in assessing disease severity, duration, and response to treatment.

Disease severity and duration

Several biomarkers of disease severity have been studied, including exacerbations with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), increased basophil CD203c expression, basopenia, eosinopenia, autologous serum skin test (ASST), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, mean platelet volume (MPV),

vitamin D, interleukin (IL)-6, IL-18 IL-17, IL-23, tumor necrosis factor alpha (TNF- α), lipocalin (LCN2), and prothrombin fragment 1 + 2 (F1+2). However, the strongest association has been demonstrated with D-dimer, CRP, F1+2, MPV, and IL-6 3,7 (Figure 1).

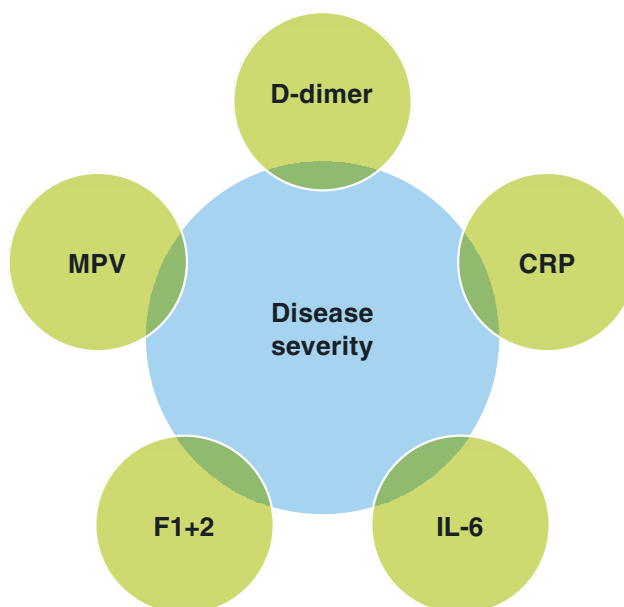
Factors such as disease severity, presence of angioedema, age, NSAID-induced exacerbation, association with CIndU, presence of thyroid autoantibodies, increased IL-6 levels, basophil high-affinity IgE receptor (Fc ϵ RI) expression, and positive ASST have been evaluated as predictors of disease duration, but with conflicting results. There is weak evidence that the presence of thyroid autoantibodies is related to longer disease duration.³⁻⁵

Some studies have demonstrated that the coagulation cascade may be activated in patients with CSU.^{8,9} Plasma markers of thrombin generation and fibrinolysis, such as D-dimer and F1+2, are elevated in patients with CSU, suggesting that, upon activation of endothelial cells, tissue factors are released with subsequent activation of the extrinsic coagulation cascade and secondary fibrinolysis. The resulting thrombin can increase vascular permeability and induce mast cell degranulation. However, there are no changes in hemostasis or a higher frequency of thrombotic events in CSU.^{8,9}

F1+2 and D-dimer levels correlate with disease activity. Mean F1+2 levels were higher in patients with CSU than in controls (2.54 [SD 2.57] nmol/L vs. 0.87 [SD 0.26] nmol/L; $p < 0.001$), with moderate or severe disease activity in 9 of 11 (82%) and 9 of 26 (35%) patients with elevated or normal F1+2 levels, respectively ($p < 0.025$). Mean plasma D-dimer levels were higher in patients than in controls (329 [SD 188] ng/mL vs. 236 [SD 81] ng/mL; $p < 0.01$), with moderate or severe disease activity in 6 of 8 (75%) and 11 of 29 (38%) patients with elevated or normal plasma D-dimer levels, respectively ($p < 0.00$).¹⁰

In a retrospective study evaluating the relationship between D-dimer, CRP, and fibrin degradation products in 82 patients with CSU, high levels of these markers were associated with greater disease activity and, conversely, a decrease in these markers was observed in controls.¹¹ In a study of 141 patients with CSU, disease activity was associated with D-dimer but not with CRP, fibrinogen, MPV, or number of platelets.¹²

A retrospective Korean study evaluated whether D-dimer, CRP, and total IgE would be associated with disease activity in adult patients with CSU ($n = 48$) or

**Figure 1**

Biomarkers of chronic urticaria severity

CRP = C-reactive protein, MPV = mean platelet volume, IL-6 = interleukin 6, F1+2 = prothrombin fragment 1 + 2.

acute urticaria ($n = 46$). D-dimer levels were higher in patients with acute urticaria (1.3 g/L) than in patients with CSU (0.7 g/L) and significantly correlated with the Urticaria Activity Score (UAS) (acute urticaria $r = 0.30$; $p < 0.001$; CU $r = 0.37$; $p < 0.05$). However, there was no significant correlation between disease activity and CRP or total IgE.¹³

In an Egyptian study, plasma D-dimer and activated factor VII (FVIIa) levels were significantly higher in patients with active CSU ($n = 30$) than in controls ($n = 30$). D-dimer levels were lower in patients with grade 1 severity and higher in those with grade 4 severity. Factor VIIa levels did not differ significantly according to disease severity grades. After complete disease remission, there was a significant drop in patients' D-dimer and FVIIa levels.¹⁴

In Brazil, D-dimer and CRP levels and the ASST and UAS were evaluated in 55 patients with CSU. Mean D-dimer levels were 0.85 (SD 0.324) mg/L. Statistical analysis showed a strong and positive relationship between UAS and D-dimer, where serum D-dimer

levels were elevated (> 0.5 mg/mL) in 22 patients; 18 of them (81.81%) were classified as having CSU with an elevated activity score. It was observed that 32.7% of patients required 3 or more medications to achieve CSU remission during follow-up.¹⁵

CRP is produced by the liver and is a sensitive serum marker of inflammation. It is elevated in several diseases, including infections, neoplasms, autoimmune diseases, cardiovascular diseases, and gastrointestinal diseases. Compared with ESR, CRP is a better marker of inflammation as it is less affected by other factors such as size, shape, and number of red blood cells, female sex, and pregnancy. CRP has proven useful in determining disease activity, prognosis, and treatment efficacy.^{7,16}

The role of inflammation has been demonstrated in studies of patients with CU. Several inflammatory biomarkers have shown an important role in disease activity and response to CSU treatment, especially CRP. Increased CRP levels were found in patients with CU and associated with other inflammatory markers

(leukocytosis, neutrophilia, and elevated levels of IL-6, C3 and C4), greater disease severity, impaired quality of life, and positive ASST.^{7,17,18}

A retrospective study was conducted in 2 centers, involving 1253 patients with CSU, with the purpose of evaluating the prevalence and relevance of elevated CRP levels. One third of the patients ($n = 418$) had high CRP levels, which were associated with positive ASST ($p = 0.009$) and hypertension ($p = 0.005$) but not with other possible causes or comorbidities of CSU. CRP correlated with disease activity ($p < 0.001$), impaired quality of life ($p = 0.026$), and inflammatory and coagulation markers ($p < 0.001$).⁷

Grzanka et al. demonstrated that IL-17 and CRP levels were significantly higher in patients with CSU than in healthy individuals. Also, there was a significant difference in IL-17 and CRP levels between patients with CSU with mild, moderate-severe symptoms and healthy individuals, with the following CRP levels, respectively (expressed as median [IQR/min-max]): 1.4 (20.92-23.55/19.28-48.60) vs. 9.8 (20.92-24.08/18.85-62.73) vs. 0.4 (0.20-0.40/0.10-0.60) mg/L ($p < 0.001$). CRP did not correlate significantly with IL-17.¹⁹

Two other studies found higher CRP levels in patients with positive ASST (5.81 [SD 4.70] and 5.31 [SD 2.74]) than in those with negative ASST (2.89 [SD 4.85] and 2.53 [SD 1.27]) and controls (2.76 [SD 4.52] and 2.34 [SD 1.38]), as well as a correlation between disease activity and CRP levels.^{20,21} Magen et al. also evaluated MPV, as some studies have indicated that MPV correlates with platelet function. Large platelets are more reactive, and the presence of large platelets in the blood is an *in vivo* indicator of platelet activity. A significant positive correlation was found between CU severity score and MPV in patients with a positive ASST ($r = 0.44$; $p = 0.001$) but not in patients with a negative ASST.²¹

Among pro-inflammatory mediators, IL-6 is a promising biomarker in CSU due to its role in promoting the inflammatory response. Elevated IL-6 levels were detected in CSU, with a positive correlation with CRP levels, and also in patients with CSU in the active stage and with moderate to severe disease.^{18,22,23} However, in a study evaluating IL-18 and IL-6 levels in patients with CSU and healthy controls, there was no statistically significant difference between the groups, unlike other studies that showed a correlation between higher levels of these cytokines and disease activity.²⁴

ASST is a non-specific test that assesses the existence of autoreactivity, that is, the presence of endogenous pro-inflammatory or wheal-inducing factors, including autoantibodies, which are triggers for mast cell and basophil degranulation. Positive ASST is correlated with the presence of IgG anti-FcεRI and IgG anti-IgE antibodies, responsible for type IIb autoimmune CSU (aiCSU), whose diagnostic criteria are as follows: (a) a positive *in vitro* bioassay demonstrating autoantibody functionality (basophil histamine release assay [BHRA] or basophil activation marker expression, such as CD63 or CD203c by flow cytometry); (b) positive autoreactivity (a positive ASST) demonstrating the *in vivo* relevance of mast cell degranulation and increased capillary permeability; and (c) a positive immunoassay for autoantibodies against FcεRIα (Western blot or ELISA) demonstrating autoantibody specificity.²⁵

Positive ASST has been associated with greater disease activity, longer duration, and basopenia,^{15,26,27} but further studies are needed. A systematic review of parameters associated with CSU duration and severity found 8 studies demonstrating an association between positive ASST and CSU severity, and 8 studies reporting no association.²⁸

Increased FcεRIα expression with upregulated CD203c expression on peripheral basophils is observed in patients with CU. Aiming to investigate whether increased basophil activation would be associated with disease activity, basophil CD203c expression was evaluated in 82 patients with CU and 21 healthy controls. Mean CD203c expression was significantly higher in patients with CU than in controls (57.5% vs. 11.6%, $p < 0.001$). Basophil CD203c expression was significantly higher in patients with severe CU than in those with non-severe CU (66.5% [SD 23.3%] vs. 54.0% [SD 23.3%], $p = 0.033$).²⁹

Autoimmune thyroid disease is frequently observed in patients with CSU, as is the presence of antithyroid antibodies. Anti-TPO IgG measurements are recommended in international urticaria guidelines to assess type IIb autoimmunity.¹ The presence of anti-TPO IgG has not been related to urticaria severity, but some studies have associated it with disease duration. A retrospective study found that 12% of patients with CSU had anti-TPO IgG, and these patients had longer disease duration than those without anti-TPO IgG. However, there was no difference in disease severity. The same study also reported that 70% of patients had positive ASST and autologous plasma skin test (APST), and both tests were associated with disease

severity.³⁰ In 2004, Toubi et al. identified that ASST and antithyroid antibodies were positive in 28% and 12% of patients with CSU, with the disease lasting longer in these patients than in those with negative ASST and anti-TPO IgG. However, there was no association with disease severity.³¹

Response to treatment

Non-sedating antihistamines at standard or high doses are recommended as first- and second-line treatment for CSU. However, up to 50% of patients are refractory to high doses of antihistamines and require other medications, such as omalizumab and cyclosporine, to achieve complete symptom control.¹ Predicting treatment efficacy before prescribing it is essential to achieve remission, or if not possible, to improve disease control, avoiding wasting time with an ineffective therapeutic regimen. However, the validation of biomarkers for this purpose remains poorly defined. Studies have been developed using CRP, D-dimer, total IgE, basophil CD203c and FcεRI expression, IL-31, ASST, and BHRA, among others.³

High disease activity and high levels of weekly UAS (UAS7), CRP, and D-dimer appear to be good predictors of refractoriness to H1-antihistamines (Figure 2). Low total IgE levels are strongly related to poor or no response to omalizumab, and good response to cyclosporine is predicted by the BHRA, as demonstrated in a systematic review.³²

Refractoriness to antihistamines

Some clinical biomarkers have been related to refractoriness to anti-H1, including the presence of comorbidities such as atopic asthma, rhinitis, rhinosinusitis, thyroid diseases, and hypertension. However, the evidence for this correlation remains weak.^{33,34}

In a retrospective study of 549 patients with CU, more than 75% of patients were refractory to anti-H1, and baseline UAS7 was the only parameter able to predict refractoriness; approximately 90% of patients with UAS7 > 16 required treatment with omalizumab or cyclosporine.³⁵ Another retrospective study of 385

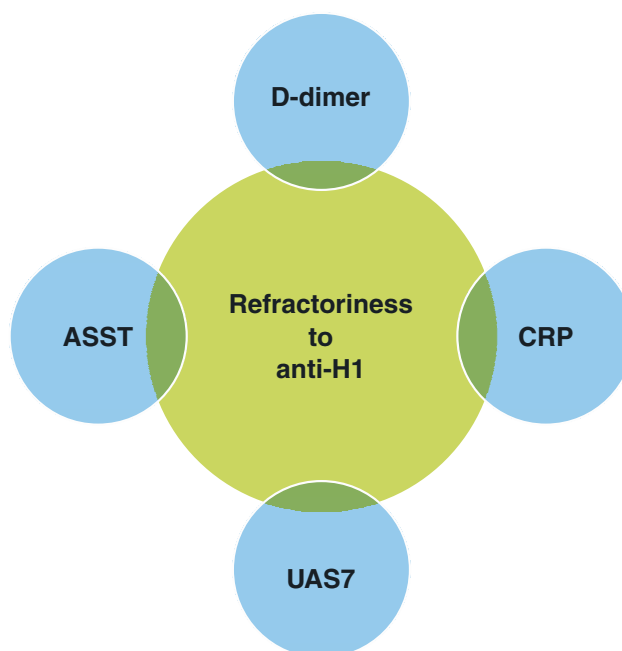


Figure 2

Biomarkers of refractoriness to antihistamines

ASST = autologous serum skin test, CRP = C-reactive protein, UAS7 = urticaria activity score 7.

patients with CSU reported that patients refractory to anti-H1 were characterized by a higher incidence of angioedema, concomitant CIndU, positive ASST, and higher baseline UAS (5.28 in the refractory group and 3.32 in anti-H1 responders). Higher CRP levels were also observed.³⁶ The finding was confirmed in a sample of 1253 patients with CSU, in which high CRP levels were also correlated with refractoriness to anti-H1.

When evaluating biomarkers of response to levocetirizine in 84 patients with CU, 7.1%, 9.5%, 12%, 31%, and 47.6% of responders had elevated levels of D-dimer, fibrinogen, ESR, CRP, and total IgE, respectively, as well as 54.8%, 26.2%, 35.7%, 54.8%, and 23.8% of non-responders, respectively.³⁷

Montjoye et al., in a prospective study of 95 patients with CSU, found elevated CRP levels in anti-H1 non-responders ($p < 0.0001$) and in more severe diseases ($p = 0.033$). Plasma D-dimer levels were also higher in non-responders ($p = 0.008$) and in patients with concomitant autoimmune disease and/or with autoantibodies ($p = 0.016$). Blood basophil counts were lower in anti-H1 non-responders ($p = 0.023$) and in patients with more severe disease ($p = 0.023$), positive ASST ($p = 0.001$), and autoimmune disease ($p = 0.057$).³⁸

Coagulation activation has been studied in the pathophysiology of CU. Tissue factor is expressed in the eosinophils present in the inflammatory infiltrate in urticaria, and thrombin is able to degranulate mast cells. Therefore, an increase in plasma levels of D-dimer, a marker of fibrinolysis, may be a potential biomarker of refractoriness to anti-H1.³⁷⁻³⁹ Asero reported that D-dimer levels were elevated in 0 of 41 patients (0%) with an “excellent” response to cetirizine, 3 of 14 (21%) with a “good” response, 3 of 5 (60%) with a “partial” response, 18 of 23 (78%) with a “poor” response, and 7 of 8 (88%) non-responders.³⁹

The role of ASST as a biomarker of anti-H1 refractoriness is still controversial. Although some studies have demonstrated this correlation,^{36,40} others have not.⁴¹ Ye et al. found that ASST can be a good marker of good response to treatment.²⁷ Chanprapaph et al. observed a correlation with the APST, but not with the ASST³⁰ (Figure 2).

Response to omalizumab

Omalizumab is a humanized anti-IgE monoclonal antibody indicated for the treatment of anti-H1-

resistant CSU that has demonstrated good efficacy and safety in clinical trials and real-life studies.¹ Response to omalizumab can be classified by the time of occurrence as fast, slow, or absent after 6 months of treatment or by type as complete (UAS7: 0), good (UAS7: 1-6), partial (UAS7: 7-15), or absent (UAS7 > 16), as proposed by Arnau et al.⁴² Furthermore, after discontinuing treatment, some patients experience relapse, which in the OPTIMA trial occurred in 50% of patients.⁴³ Determining biomarkers of initial response and relapse profiles is necessary in the discussion with patients about treatment indication and their expectations⁴⁴ (Figure 3).

Low serum total IgE levels have been associated with poorer response to omalizumab treatment. Straesser et al. evaluated serum IgE levels in patients with CSU divided into 4 quartiles. The odds ratio for response to omalizumab was 13.8 for patients with serum IgE levels at the 75th percentile (> 168.0 IU/mL) than for those at the 25th percentile (< 15.2 IU/mL) ($p < 0.001$).⁴⁵ Marzano et al. reported similar data in a study of 470 patients in which responders had mean total IgE levels of 131.6 kUA/L and non-responders of 42.1 kUA/L ($p < 0.0001$).⁴⁶

Baseline total IgE levels above 43.0 IU/mL that increased by 2-fold or more at week 4 of omalizumab treatment were correlated with improvement in CSU at week 12 of treatment.⁴⁷ Furthermore, baseline total IgE levels appear to correlate with time to CSU relapse after discontinuation of omalizumab treatment. Higher IgE levels were associated with shorter time to relapse of CSU symptoms after discontinuation of omalizumab.⁴⁸ Cugno et al. demonstrated that not only IgE but also baseline D-dimer levels were higher in responders than in non-responders to omalizumab in CSU.⁴⁹ Regarding D-dimer, this finding was not reported by Marzano et al.⁴⁶ Asero et al. evaluated D-dimer levels before and 3 weeks after omalizumab administration and found no difference between responders and non-responders in baseline D-dimer levels. However, responders showed a significant drop after the second dose, indicating that D-dimer may be a good marker of efficacy.⁵⁰ Other markers, such as a decrease in IL-31 and CRP levels and an increase in basophil levels, were also identified as markers of efficacy.^{38,51} IL-31 is produced primarily by activated Th2 lymphocytes and skin mast cells and plays an important role in the induction of chronic skin inflammation, especially pruritus. Elevated levels were found in patients with CSU, but with no relationship to severity.⁵¹

Markers of type IIb autoimmunity, such as positive ASST, BHRA, and basophil activation test (BAT) and basopenia, have been associated with delayed or no response to omalizumab.⁵²

ASST and BHRA are used in the diagnosis of autoimmune CU by assessing the presence of serum autoreactivity and autoantibody functionality, respectively. Positive ASST and BHRA have been associated with a slow response to omalizumab, but the evidence remains inconsistent. In the study by Gericke et al., an analysis of the profile of omalizumab responders showed that most BHRA-positive patients responded only after the second injection, with a median time to response of 29 days, whereas BHRA-negative patients had a median time to response of 2 days. Only 1 of 39 fast responders was BHRA-positive, whereas 8 of 17 slow responders were BHRA-positive ($p < 0.0001$). Regarding the ASST, 12 of 33 fast responders and 10 of 13 slow responders showed a positive ASST ($p < 0.012$).⁵³

Another marker that has been the target of several studies is basophil FcεRI expression. Deza et al. described that basophil FcεRI expression levels before omalizumab treatment were significantly higher in responders than in non-responders. Also, after initiating omalizumab, there was a significant reduction of almost 90% in basophil FcεRI expression about 1 month after the first dose, with a lower reduction in non-responders than in responders, as well as speed response, which showed the same response profile.^{54,55}

The expression of some receptors on the surface of basophils has been related to disease severity. Ye et al. showed that basophil CD203c expression was higher in patients with severe CSU, suggesting that the quantification of basophil activation and CD203c expression measured by flow cytometry may be used as a potential predictor of CSU severity.²⁹ Also investigated as a marker of response to omalizumab and disease activity, upregulation of CD203c was present in 18/41 individuals (43.9%), and omalizumab was effective in 29/41 patients with CU (71%). Of the 18 individuals demonstrating CD203c-upregulating activity, only 9 (50%) experienced clinical improvement with omalizumab. However, of the 23 without CD203c-upregulating activity, 20 (87%) had a satisfactory clinical response ($p = 0.02$). Therefore, having a negative result in the expression of these markers predicts a greater likelihood of responding to omalizumab.⁵⁶

UAS7, a tool that assesses disease activity over 7 days, is used to assess disease severity in daily practice and in clinical studies, and also to assess response to treatment. A study evaluating UAS7 as a predictor of relapse after discontinuation of omalizumab demonstrated that patients with high baseline UAS7 and late response experienced rapid relapse⁵⁷ (Figure 3).

Response to cyclosporine

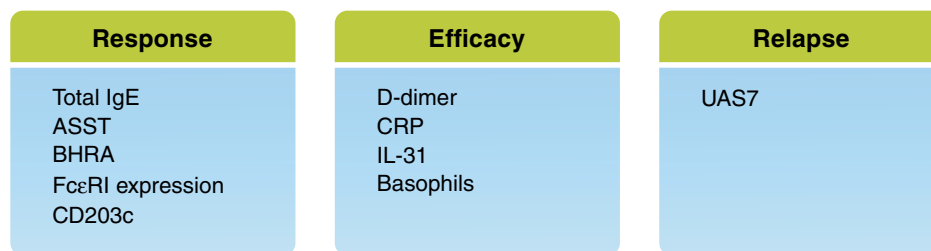
For non-responders to omalizumab, the recommended treatment is cyclosporine, an immunosuppressant that has a moderate effect on the inhibition of mediator release from mast cells. In contrast to other immunosuppressants with cytotoxic action, cyclosporine does not suppress the bone marrow and has no known risk of teratogenicity in humans. Its efficacy in combination with second-generation H1-antihistamines has been demonstrated in clinical trials, but it is used as third-line therapy due to a higher incidence of adverse effects, which, however, is lower than that with long-term use of corticosteroids.¹⁰

A systematic review showed strong evidence that positive BHRA and the presence of low total IgE levels are predictors of a good response to cyclosporine.³² Grattan et al. conducted a randomized clinical trial that demonstrated a positive baseline BHRA in 72% of cyclosporine responders (vs. 11% of non-responders).⁵⁸ Two other studies showed that positive BHRA is a predictor of remission with cyclosporine treatment,^{59,60} but ASST does not appear to be a good biomarker.⁵⁸

Serum IgE levels were significantly lower in cyclosporine responders (43.0 IU/mL) than in non-responders (148.5 IU/mL) ($p < 0.001$), being negatively correlated with the decrease in UAS7 at 3 months of treatment.⁶¹ Endo et al. showed that low baseline total IgE levels were associated with low UAS7 after cyclosporine treatment.⁶²

Asero reported that D-dimer levels showed a highly significant negative correlation with response to cyclosporine ($p < 0.017$); with 10 of 11 (91%) patients with normal plasma D-dimer levels vs. 7 of 18 (39%) patients with elevated plasma D-dimer levels showing a completely successful response to treatment.⁶³

It is clear that CU is a heterogeneous disease with different phenotypes, possible clinical characteristics, associated factors, and different clinical course, as well as different degrees of response to the

**Figure 3**

Biomarkers of response to omalizumab

ASST = autologous serum skin test, BHRA = basophil histamine release assay, FcεRI = high-affinity IgE receptor, CRP = C-reactive protein, IL-31 = interleukin 31, UAS7 = urticaria activity score 7.

treatments administered. It is particularly relevant to identify biomarkers able to classify patients according to their phenotype, possibly identifying underlying immunological mechanisms in order to stratify patients according to disease severity and prognosis and to identify the best responders to any therapy, especially to biological products. We highlight the importance of using accessible biomarkers in clinical practice, such as CRP, D-dimer, anti-TPO, total IgE, and UAS7. However, further prospective studies are needed to confirm these predictors and identify others.

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Profile of patients with chronic spontaneous urticaria treated with omalizumab in Chapecó, south of Brazil

Perfil de pacientes com urticária crônica espontânea submetidos ao tratamento com omalizumabe em Chapecó, SC

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ABSTRACT

Introduction: Chronic spontaneous urticaria is a disease characterized by erythematous maculopapular eruption, associated with itching and angioedema, that has no recognized external stimulus and is difficult to control. First- and second-line treatments, available through the Brazilian Unified Health System, do not yield meaningful results, and patients become refractory. Omalizumab, considered a third-line treatment and not widely available through the Brazilian Unified Health System, may yield meaningful results in halting disease symptoms. **Objective:** To evaluate patients with chronic spontaneous urticaria who have used or are using omalizumab. **Methods:** We conducted a cross-sectional case series observational study with a review of the medical records of 34 patients with chronic spontaneous urticaria treated with omalizumab at the Eye Institute of Santa Catarina, south of Brazil. **Results:** Most patients with chronic spontaneous urticaria receiving omalizumab were female (76.5%) with a mean age of 41 years. The disease most commonly associated with chronic spontaneous urticaria was depression (38.2%). Omalizumab treatment success was measured with the Urticaria Activity Score (UAS7). Based on data extracted from the medical records, all 34 patients had a score greater than 35 before treatment. After receiving omalizumab, 32 patients managed to reach a score of 0, differing only in the duration of treatment. **Conclusion:** Chronic spontaneous urticaria is an incurable, highly refractory disease, but its symptoms can be reduced mainly with the use of omalizumab, which proved to be effective in the cases analyzed here.

Keywords: Chronic spontaneous urticaria, omalizumab, monoclonal antibodies.

RESUMO

Introdução: A urticária crônica espontânea é caracterizada por lesões máculo-papulares eritematosas, associadas a prurido e angioedema, que não possui estímulo externo reconhecido e de difícil controle. A primeira e a segunda linha terapêutica, disponibilizadas pelo Sistema Único de Saúde, não apresentam resultados significativos, os quais se tornam refratários. O omalizumabe, considerado terceira linha terapêutica e que não é amplamente disponibilizado pelo Sistema Único de Saúde, pode apresentar resultado significativo na interrupção dos sintomas da doença. **Objetivo:** O presente estudo tem como objetivo avaliar pacientes com urticária crônica espontânea que usaram ou estão em uso de omalizumabe. **Métodos:** Trata-se de um estudo observacional transversal do tipo série de casos, cuja análise foi feita através dos prontuários, com população de 34 pacientes com urticária crônica espontânea submetidos ao tratamento com omalizumabe no Instituto de Olhos de Santa Catarina (IOSC). **Resultados:** Constatou-se no estudo que a maioria dos pacientes com urticária crônica espontânea em uso de omalizumabe é constituída do sexo feminino (76,5%) e idade média de 41 anos. A doença mais associada à urticária crônica espontânea foi depressão (38,2%). O sucesso do tratamento com omalizumabe é medido pelo questionário UAS7 (*Urticaria Activity Score*), o qual, segundo os dados dos prontuários, todos os pacientes apresentavam resultado maior que 35 pontos antes do uso da medicação, e 32 conseguiram alcançar um índice de 0 após o uso do omalizumabe, variando apenas no tempo de tratamento. **Conclusão:** A urticária crônica espontânea é uma doença que não tem cura e possui alta refratariedade, mas pode ter seus sintomas reduzidos, principalmente com o uso do omalizumabe, que se mostrou eficiente nos casos analisados.

Descritores: Urticária crônica, omalizumabe, anticorpo monoclonal.

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Introduction

Chronic urticaria is a highly morbid disease that affects between 0.5% and 1% of the population and is often difficult to control. It is characterized by erythematous maculopapular lesions associated with pruritus, which may present angioedema and generally lasts less than 24 hours.¹ Urticaria can be classified into 2 main groups: acute urticaria (AU), which lasts 6 weeks or less, and chronic urticaria (CU), which lasts 6 weeks or more. Additionally, chronic urticaria can be divided into chronic inducible urticaria (CIndU), which has an identified exogenous causal factor, and chronic spontaneous urticaria (CSU), when there is no recognized external trigger, and both forms can occur simultaneously in the same individual.² The diagnosis of CSU and all forms of CUs are essentially clinical, and there are no specific complementary tests.

Treatment can be challenging. Second-generation H1-antihistamines are considered the first-line therapy for CSU. They are minimally or non-sedating and free of anticholinergic effects and have a good safety profile, unlike first-generation H1-antihistamines, which are currently not recommended due to their adverse effects.³ However, although these medications are available in Brazil's public health system (SUS), they have a high added value and treatment may fail, requiring a fourfold dose in an attempt to achieve the intended effect.⁴ Even so, a large proportion of patients remain refractory to H1-antihistamines and have to resort to second- or third-line treatments, which include omalizumab, cyclosporine, or montelukast.¹

Cyclosporin is an immunosuppressive and anti-inflammatory medication. It has a better risk-benefit ratio than corticosteroids, though the incidence of side effects such as nephrotoxicity and hypertension are a cause for concern and require monitoring.⁵ A study found the medication to be effective in 44% of patients with moderate to severe urticaria.⁶

Montelukast, a leukotriene receptor antagonist, is perhaps the most cost-effective of the medications. However, high-quality clinical studies have not provided evidence of the efficacy and safety of this medication. Even so, it is used in some refractory cases of CSU.⁷

The use of systemic corticosteroids in exacerbations of CU is recommended for no longer than ten days and in the lowest possible dose, given the potential adverse effects of long-term treatment.¹

CSU has an autoimmune component associated with Immunoglobulin-E, which the immunobiological

omalizumab (Anti-IgE) may have some effect, as it has a direct action on the pathophysiological mechanisms of the disease; it is considered the third-line treatment option to treat CSU.³ However, even though the medication is safe with positive results, it has a high cost, ranging from R\$1,795.83 to R\$2,244.79 per vial, depending on the dose required, and SUS hardly makes it available, except for the treatment of severe asthma.⁸

The patient's routine is affected due to unpredictable and chronic outbreaks and compromised body image, especially caused by pruritus and angioedema, which affect the performance of daily activities and the quantity and quality of sleep, causing direct costs in medication consumption, the use of health care services, and indirect costs associated with lower school and professional performance.¹ This study aims to evaluate patients with CSU who used or are currently using omalizumab, as well as to verify the positive and adverse effects and impacts in different cases of CSU, and to compare the efficacy of omalizumab with other medications in the treatment of CSU.

Material and methods

This is an observational case-crossover study, whose analyzed population consisted of 34 patients treated with omalizumab and with CSU, from the *Instituto de Olhos Santa Catarina (IOSC) - Hospital Dia*.

The sample included patients treated with omalizumab and with CSU between July 2018 and May 2021. Patients who had not completed 3 months of treatment with omalizumab or who did not follow the treatment protocol properly were excluded.

Data were collected from patients with CSU who had taken omalizumab, through medical record analysis to identify their clinical evolution. Subsequently, information was retrieved from medical records based on a questionnaire about the disease and the use of the medication. This information was held in confidence as per a confidentiality agreement.

Data such as sex, age, time since diagnosis of CSU, medications used before and associated with omalizumab, symptoms and diseases associated with CSU, and the time required for omalizumab to take effect were analyzed. The Urticaria Activity Score (UAS7), which assesses the symptoms and intensity

of CSU over a 7-day period, was also analyzed. It was previously applied by the attending physician to patients before and after the use of omalizumab and recorded in their medical records.

The results were calculated as means, modes, and medians of the variables mentioned above, using Microsoft Excel and Epi-Info.

The project was developed in accordance with CNS Resolution No. 466/201223 and Resolution No. 510/201624, analyzed by the Research Ethics Committee Involving Human Beings - CEP/UNOCHAPECÓ and approved according to Opinion No. 4.822.997 (CAAE 48046721.2.0000.0116).

Results and discussion

CSU manifestations result from the release of pro-inflammatory mediators from mast cells found in the dermis of mucous membranes. Different factors can induce mast cells, from the activation of nerve endings and vessels in the dermis, recruiting inflammatory cells such as endothelial cells, eosinophils, and even mast cells. CSU most commonly presents clinical signs such as erythematous papules, pruritus, and angioedema. The papules show mast cell and eosinophil degranulation, endothelial cell activation, vascular proliferation, and activation of blood coagulation. In addition, CSU produces a proliferated cytokine environment, indicating an activation of the innate interleukin (IL) response, especially IL-33 and IL-25.¹

The study included 34 patients who had CSU and had used omalizumab between July 2018 and May 2021. As shown in Table 1, 26 (76.5%) patients were women and 8 (23.5%) were men. The mean age (SD) was 41 (5.66) years. The age group with the most patients was 41 to 60 years (44.1%). The results are consistent with Ozlem et al.,⁹ who also found that women were prevalent and the mean age was 44.3 years. This age group is also similar to that of Souza et al. who reported a higher prevalence between 20 and 50 years of age.¹⁰

Interestingly, 4 patients (11.8%) had a family history of CSU, all third-degree relatives, although there is still no data to suggest that CSU has an associated genetic inheritance. Although most patients (82.4%) had a history of CSU progression up to 10 years, the mean age (SD) was 4 (10.38) years.

As shown in Table 2, the most common symptom associated with CSU was pruritus, reported by 27

Table 1

Clinical and demographic characteristics of patients with chronic spontaneous urticaria (CSU)

Variable	n = 34	%
Sex		
Female	26	76.5
Male	8	23.5
Age group		
Up to 20 years	2	5.9
21-40 years	12	35.3
41-60 years	15	44.1
61-72 years	5	14.7
Time since CSU		
Up to 10 years	28	82.4
More than 10 years	6	17.6
Family history of CSU		
Yes	4	11.8
No	32	88.2

(79.4%) patients, followed by angioedema (55.9%), pain in the lesions (23.5%), positive dermographism (14.7%), and oropharyngeal edema (11.8%). The least common symptoms were joint pain (5.9%), changes in sleep (5.9%), abdominal pain (4.2%), and fever (4.2%).

The high prevalence of pruritus as a symptom of CSU is mainly due to the release of histamine and inflammatory cytokines. Acute pruritus is primarily mediated by histamine H1 and H4 receptors, which trigger other symptoms such as edema and erythema.¹¹

Although histamine is the most common mast cell mediator in CSU, the ineffectiveness of first-line medications shows that other pro-inflammatory mediators are involved, such as platelet activating factor, leukotrienes, prostaglandins, chemokines, and cytokines, among others. These mediators are increased in the peripheral blood during urticarial activity.¹

Angioedema was higher than the findings of Souza et al.¹⁰ (2019), who reported 28.6% of patients

with angioedema. As for the pathophysiology of angioedema and pruritus in CSU, it is related to the release of histamine as an inflammatory mediator, called histaminergic angioedema. It has a better prognosis and generally responds well to treatment with antihistamines and corticosteroids.¹² This study found less positive dermographism than Duarte P.P., whose sample included 20%.¹³

Table 2 also shows that the most prevalent chronic diseases affecting the patients studied concomitantly

with CSU were depression (38.2%), hypothyroidism (17.8%), hypertension (14.7%), dyslipidemia (14.7%), and anxiety (11.8%). Neuropathic pain, vasculitis, rhinitis, cardiovascular disease, thrombosis, angina pectoris, and hepatitis B showed results below 8.8%. The results for depression were higher than those of Vieira,¹⁴ whose population had a prevalence of psychiatric illnesses of 22.5%, including depression and/or panic disorder and/or anxiety. As for anxiety, the rate of patients is similar to the study above.

Table 2

Diseases associated with chronic spontaneous urticaria (CSU) in patients taking omalizumab

Variable	Female	Male	Total	%
Diseases associated with CSU				
Depression	10	3	13	38.2
Hypothyroidism	4	2	6	17.8
Hypertension	4	1	5	14.7
Dyslipidemia	4	1	5	14.7
Anxiety	3	1	4	11.8
Neuropathic pain	2	1	3	8.8
Vasculitis	1	0	1	4.2
Rhinitis	2	0	2	5.9
Cardiovascular disease	1	1	2	5.9
Thrombosis	1	0	1	4.2
Angina Pectoris	1	0	1	4.2
Hepatitis B	1	0	1	4.2
Signs and symptoms associated with CSU				
Pruritus	20	7	27	79.4
Angioedema	15	4	19	55.9
Pain in the lesions	7	1	8	23.5
Dermographism +	3	2	5	14.7
Oropharyngeal edema	4	0	4	11.8
Joint pain	2	0	2	5.9
Sleeping disorders	2	0	2	5.9
Abdominal pain	0	1	1	4.2
Fever	1	0	1	4.2

The study by Farril-Romanillos et al.¹⁵ (2019) found better results than this study in relation to the association of CSU with hypothyroidism, with 82% of the patients studied having both diseases. However, 28% of these patients had positive antibodies and were all women, which also differs from ours, in which 2 patients (5.9%) were men.¹⁵ This association between CSU and hypothyroidism occurs because mast cells are activated in urticaria and are responsible for releasing inflammatory mediators such as histamine, mainly due to the binding of various types of IgE antibodies, including anti-thyroperoxidase IgE (anti-TPO) to their surface. These antibodies sensitize mast cells and induce degranulation after exposure to the specific circulating antigen, and anti-TPO are the same as those produced against the thyroid in diseases that cause hypothyroidism, in which they are released as a result of autoimmune damage to thyroid. Therefore, we cannot say that there is only 1 relationship between both diseases, but rather that they coexist.¹⁶

The most prevalent aggravating factors for CSU were non-steroidal anti-inflammatory medication use (23.0%), viral infection (15.4%), summer (15.4%), sweating (11.5%), and stress (7.7%).

The percentages in the table do not total 100% because some patients have more than one disease and/or associated symptom. These medications cannot be said to directly induce CSU due to the prevalence of the disease's autoimmune factor; however, these factors can be powerful triggers for worsening the clinical condition.

All the patients followed the recommended standard of treatment, took second-generation antihistamines, had their doses boosted up to 4 times, and then resorted to omalizumab as a third-line treatment. In addition, 4 patients tried to use fourth-line medications before omalizumab, such as cyclosporine and montelukast, but their condition failed to improve.

Omalizumab is a humanized anti-IgE monoclonal antibody that is capable of reducing the release of inflammatory mediators from CSU. It acts by binding to the C3 domain of free IgE, preventing this immunoglobulin from binding to the receptors present on the membranes of mast cells.¹⁷ Omalizumab also has the ability to reduce levels of free IgE and high-affinity IgE receptors, which are located on the surface of mast cells and basophils.¹⁸

Omalizumab is administered subcutaneously at intervals of 2 to 4 weeks, depending on the patient's needs. In Brazil, SUS has widely approved it since 2012 as the fifth step in the treatment of severe asthma refractory to the usual medications.¹⁹

As Table 3 shows, most patients (41.2%) took up to 1 year to start omalizumab after being diagnosed with CSU. The mean (SD) was 3.8 (59.1) years. It took a mean (SD) of 2.3 (1) months to start having an effect. Most patients (32.4%) took 3 months to show a response. This differs from the results of Labrador-Horrillo et al.²⁰ (2013) and Büyüköztürk et al.²¹ (2012), whose patients (53.4%) took 1 week to respond to omalizumab.

Another 2 patients did not respond to the medication, as they discontinued it because it was inaccessible to the general public, and they could not afford to continue with the treatment. In the study by Ensina et al.²² (2016), 2 patients also discontinued the medication for the same reason. As this is also a Brazilian study, it confirms that users find the high cost and difficulty of obtaining the medication in the SUS a limitation.²²

Only 1 patient had an adverse effect (hypotension) associated with the use of omalizumab, and it was later found that their urticaria was due to vasculitis, for which the medication has no effect. Most of the patients (35.3%) had been taking the medication for 2 years, whereas the mean was 1 year.

As for the success of treatment with omalizumab, as measured by the UAS7 score, all the patients scored more than 35 points before using first-line medication, up to 25 points even after using second-generation antihistamines, and 32 managed to reach an index of 0 after using omalizumab, only varying the length of treatment. These results showed that omalizumab was more effective than the study by Su et al.²³ (2020), which reported that the mean UAS7 score before taking omalizumab was 31 points, and after 6 months of taking the medication, patients achieved a mean score of 3.9, in a sample of 50 patients.

The high UAS7 scores before taking omalizumab, even after a maximum dose of antihistamines, reflect the considerable worsening of patients' quality of life, since this score measures the signs and symptoms they experience during a week of CSU exacerbation. As a consequence, in addition to self-medication and taking improper medication, emergency health services are in high demand to try to relieve the

worst symptoms, such as angioedema, pruritus, and oropharyngeal edema, which consequently lead to reduced productivity.

Figure 1 shows the medications used in combination with omalizumab in exacerbations of CSU. Most patients (67.3%) took second-generation antihistamines, and 8 patients (16.3%) did not need any associated medication. In relation to the studies by Su et al.²² (2020), our results show that fewer patients required simultaneous use of antihistamines and omalizumab, since the comparative study reported that 46% of patients took antihistamines regularly and 44% did so irregularly and for a short time, totaling 90% of the sample. In addition, only 5 patients in the other study required no treatment associated with omalizumab, which is less than our findings.

Conclusion

CSU is a disease with high morbidity, caused by autoimmune disorders, with periods of worsening and remission, whose exacerbation can last for years. The profile of patients affected by the disease is mostly made up of young women of working age who have taken up to 10 years to be diagnosed with CSU, leading to decreased quality of life during this period and less productivity. In many cases, these patients are not responsive to the usual first- and second-line treatments.

This study showed that omalizumab, a third-line medication for CSU, was effective in controlling patients' symptoms, some as early as when the first dose was administered, reducing the use of antihistamines. As a result, this immunobiological reduced self-medication, the misuse of other medications, and health costs, such as frequent visits to emergency departments and other specialized consultations.

Table 3

Analysis of the use of omalizumab in patients with CSU

Variable	n = 34	%
Time between CSU diagnosis and initiation of omalizumab		
Up to 1 year	14	41.2
2-5 years	12	35.3
6-10 years	4	11.8
More than 10 years	4	17.6
Response time after initiating omalizumab		
1 month	8	23.5
2 months	10	29.4
3 months	11	32.4
4 months	3	8.8
No response	2	5.9
Time of treatment with omalizumab		
Less than 1 year	5	14.7
1 year	14	41.2
2 years	12	35.3
3 years or more	3	8.8

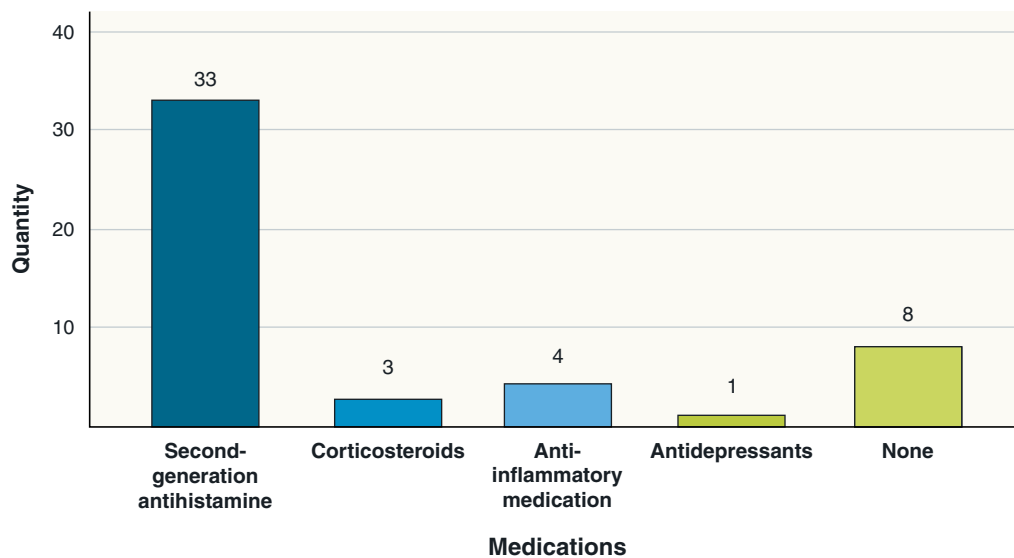


Figure 1
Medications associated with treatment with omalizumab

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Chronic granulomatous disease: clinical characteristics, follow-up, and therapy of 5 pediatric patients

Doença granulomatosa crônica: características clínicas, seguimento e terapêutica de cinco pacientes pediátricos

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ABSTRACT

Introduction: Chronic granulomatous disease (CGD) is characterized by a defective microbicidal capacity of phagocytic cells (monocytes and neutrophils) with high mortality if not early diagnosed. Patients have recurrent or severe infections and are susceptible to granulomas in visceral organs, autoimmune diseases, and inflammatory bowel diseases. **Objective and Method:** To report the clinical features and treatment of 5 patients with CGD. **Results:** Five patients, 3 boys, with median ages at symptom onset and diagnosis of 8 months and 48 months, respectively, were followed for 10 years. Pneumonia (5/5) and mycobacterial disease (3/5) were the most common initial manifestations. Pulmonary changes were observed in all cases. Mutations in the *CYBB* and *NCF1* genes were identified in 3 cases. All patients received antibiotic prophylaxis. Three patients underwent a hematopoietic stem cell transplant (HSCT) at 7, 18, and 19 years, with current survival of 4 to 5 years. **Conclusion:** Careful monitoring for severe infection with prompt treatment was crucial for survival. Even though HSCT was performed in late adolescence, it promoted the cure of CGD in 3 patients.

Keywords: Chronic granulomatous disease, phagocyte, NADPH oxidases, bone marrow transplantation.

RESUMO

Introdução: A doença granulomatosa crônica (DGC) é caracterizada por um defeito na capacidade microbicida das células fagocíticas (monócitos e neutrófilos), com alta mortalidade se não diagnosticada precocemente. Os pacientes apresentam infecções recorrentes ou graves, suscetibilidade a granulomas em órgãos profundos, doenças autoimunes e doença inflamatória intestinal. **Objetivo e Método:** Relato de aspectos clínicos e do tratamento de cinco pacientes com doença granulomatosa crônica. **Resultados:** Cinco pacientes, três meninos, medianas de idade no início dos sintomas e diagnóstico de 8 meses e 48 meses, respectivamente, foram estudados por um período de 10 anos. Pneumonia (5/5) e doença micobacteriana (3/5) foram as manifestações iniciais mais comuns. Alterações pulmonares foram observadas em todos os casos. Mutações nos genes *CYBB* e *NCF1* foram identificadas em três casos. Antibioticoprofilaxia foi instituída em todos os pacientes e três foram submetidos ao transplante de células tronco-hematopoiéticas (TCH), aos 7, 18 e 19 anos e com sobrevida atual entre 4 a 5 anos. **Conclusão:** O monitoramento cuidadoso de infecções graves com tratamento imediato foi crucial para a sobrevivência. O TCH, mesmo ao final da adolescência, promoveu a cura da DGC em três pacientes.

Descritores: Doença granulomatosa crônica, fagócitos, NADPH oxidases, transplante de medula óssea

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Introduction

Chronic granulomatous disease (CGD) is a severe primary immunodeficiency or inborn error of immunity characterized by defective microbicidal function in phagocytic cells (neutrophils and monocytes).^{1,2} CGD has an estimated incidence of 1 in 200,000 live births.² Symptom onset occurs in the first years of life, with severe infections in the skin, respiratory tract, lymph nodes, liver, and bones, in addition autoimmune diseases and susceptibility to granuloma formation in many organs.²⁻⁴

CGD is caused by mutations in a gene that encodes proteins of the nicotinamide adenine dinucleotide oxidase enzyme complex in phagocytic cells. The *CYBB* gene, which encodes the gp91phox protein, causes X-linked CGD, and approximately 70% of CGD cases are X-linked.^{1,2} There are also autosomal recessive forms resulting from mutations in the *NCF1*, *NCF2*, *CYBA*, *NCF4*, and *CYBC1* genes.^{1,3}

Diagnosis is based on: (I) clinical criteria, including severe bacterial and/or fungal infection (abscesses, osteomyelitis, lymphadenitis), recurrent pneumonia, lymphadenopathy and/or hepatomegaly and/or splenomegaly, obstructive/diffuse granulomas (gastrointestinal or urogenital tract), and chronic inflammatory manifestations (colitis, liver abscess, and fistula formation)⁴; and (II) laboratory criteria, including phagocyte function according to the nitro blue tetrazolium test (optical microscopy) or a flow cytometry assay using dihydrorhodamine,^{2,4} or identifying mutation in a gene associated with CGD.¹⁻³ or a definitive diagnosis, at least 1 clinical and 1 laboratory criterion are necessary.⁴

Conventional treatment for CGD is prophylaxis with trimethoprim-sulfamethoxazole (5 mg/kg/day of trimethoprim) and itraconazole 100 mg daily for patients < 13 years old or < 50 kg; 200 mg daily for those ≥ 13 years or ≥ 50 kg.^{2,3} However, the only curative treatment is hematopoietic cell transplantation (HCT).^{2,3} In Brazil, data on HCT in CGD are scarce.^{5,6} In this study, we describe 10-year clinical follow-up in 5 pediatric cases, highlighting successful HCT in 3 patients.

Description

Five patients with CGD were followed up in the immunology service of a tertiary pediatric hospital in the Federal District. Data were collected from patient records between 2011 and 2021. The confirmatory

tests were performed in cooperation with the University of Brasília's cellular immunology laboratory for the nitro blue tetrazolium test and the University of São Paulo's human immunology laboratory for the dihydrorhodamine tests and genetic analysis. This study was approved by the Plataforma Brasil Research Ethics Committee.

Clinical features

Three of the 5 patients were boys (60%); the median age at symptom onset and diagnosis was 8 and 48 months, respectively. Severe pneumonia was the main initial clinical manifestation of the disease, being observed in all cases. One child (P-1) had a history of early deaths in the family due to pneumonia (2 maternal uncles, 5 maternal cousins, and 1 brother) (Table 1). One patient (P-3) was referred from the onco-hematology service due to autoimmune hemolytic anemia associated with severe pneumonia. Prior to diagnosis, all patients required hospitalization due to infection; all are currently alive.

Complementary laboratory tests

In the initial immune system assessment, hypergammaglobulinemia⁷ was observed in 4 of the 5 patients. CD3+ T lymphocytes were elevated in 2 patients (P-1 and P-3), and the absolute number of natural killer cells⁸ was low in all 5 (Table 1). Tests to assess the microbicidal capacity of neutrophils (nitro blue tetrazolium or dihydrorhodamine) and/or genetic sequencing were performed to confirm diagnosis in all patients (Table 1). Two patients presented the following mutations in the *CYBB* gene: c.951T>A, in exon 8 (P-1) and c271c>T in exon 3 (P-4), confirming the diagnosis of X-linked CGD. One patient (P-3) presented the autosomal recessive form, with a c.75_76delGT mutation in exon 2 of the *NCF1* gene.

Complementary radiological exams

In all patients, pulmonary sequelae were assessed with chest computed tomography at diagnosis and every 2 years thereafter. All patients had abnormal results on examination, and 3 have had them since diagnosis (atelectasis [P-1] and pneumonia [P-2 and P-3]). The most recent radiological findings included: bronchiolitis obliterans (P-1 and P-5), bronchiectasis (P-2 and P-3), ground glass opacity (P-1, P-3 and P-4), and pulmonary nodules (P-1 and P-4).

Table 1

Clinical and laboratory characteristics of patients with chronic granulomatous disease treated at a pediatric hospital in the Federal District of Brazil

Patient	P-1	P-2	P-3	P-4	P-5
Sex	M	F	F	M	M
Current age (years)	22	21	11	23	21
Consanguinity	No	No	Yes	No	No
Family history	Yes	No	No	No	No
Onset of symptoms	18 months	8 months	23 dias	4 dias	12 months
Age at diagnosis	48 months	96 months	36 months	9 months	228 months
Initial clinical picture	PNM	PNM, TB, sepsis, fungal meningitis	UTI, PNM+DP AHA	Reaction to BCG vaccine, UTI, PNM	PNM, intestinal TB
Clinical picture at follow-up	TB, abscess, esophageal granuloma, fungal PNM	Osteomyelitis	PNM +DP Skin abscess Fungal PNM	Skin abscess PNM Pulmonary granuloma	Oral thrush BOOP
Microorganism	Gram positive <i>Neisseria spp.</i>	<i>C. albicans</i> Zigomiceto <i>Aspergillus sp.</i>	<i>S. epidermidis</i> , <i>B. cepacea</i>	<i>Enterobacter</i> <i>S. aureus</i> <i>E.coli</i> <i>C. albicans</i>	NI
Leukocyte / μ L	18,200	5500	10,400	6300	9500
Lymphocyte / μ L	6734	1300 ↓	6400	2268	2565
Neutrophil/ μ L	10,010	3600	2500	3213	5510
IgG (mg/dL)	1020	2290 ↑	1510 ↑	1043 ↑	1640 ↑
IgM (mg/dL)	161 ↑	286 ↑	286 ↑	82	146
IgA (mg/dL)	332 ↑	357 ↑	277 ↑	226	641 ↑
IgE (mg/dL)	3.7	2240 ↑	26.3	410	274
CD3+/ μ L	2217 ↑	1009 ↓	2849	1083 ↓	ND
CD4+/ μ L	966	512 ↓	1406	560 ↓	494
CD8+/ μ L	1209 ↑	560	1226	464	227 ↓
CD19+/ μ L	179	16 ↓	188 ↓	260 ↓	121 ↓
CD56+/ μ L	131 ↓	48 ↓	14 ↓	125 ↓	28 ↓
Functional test	NBT + DHR	NBT + DHR	NBT + DHR	NBT	DHR
Mutated gene	<i>CYBB</i>	–	<i>NCF1</i>	<i>CYBB</i>	–

AHA = autoimmune hemolytic anemia, BOOP = bronchiolitis obliterans organizing pneumonia, DHR = dihydrorhodamine oxidation test, NBT = nitro blue tetrazolium, NI = not isolated, PD = pleural effusion, PNM = pneumonia, TB = tuberculosis, UTI = urinary tract infection; ↑ and ↓ = values above or below the reference standard for the Brazilian population.^{7,8}

Follow-up and therapy

In all patients, prophylaxis with trimethoprim-sulfamethoxazole and antifungals was applied according to recommendations.² Itraconazole was the antifungal of choice. Ketoconazole and fluconazole were initially used in two patients (P-1 and P-2) and were later replaced with itraconazole. Liposomal amphotericin B and voriconazole were prescribed as specific treatments for disseminated fungemia and fungal pneumonia in 2 patients (P-1 and P-2) (Table 1). Interferon-gamma was used in 2 patients (P-1 and P-4). All patients had infectious conditions

during follow-up that required short-term therapeutic intervention.

Three of the patients had a confirmed genetic defect and a more severe clinical condition (P-1, P-3 and P-4; aged between 7 and 19 years) and underwent HCT at the Federal University of Paraná University Hospital (Table 2). Their current post-HCT survival is 4 years and 4 months (P-1), 4 years and 11 months (P-3), and 5 years (P-4). In all cases, the graft was accepted without immunosuppressive treatment. One patient had a late rejection episode and underwent a successful second transplant. All patients had normal dihydrorhodamine test results after HCT.

Table 2

Patients with chronic granulomatous disease (CGD) who underwent hematopoietic cell transplantation

Patient	P-1	P-3	P-4
Sex	M	F	M
HCT age (years)	19	7	18
Donor type and compatibility	Haploidentical, compatible 5/10	Unrelated, compatible 10/10	Unrelated, compatible 10/10
Cell source	PBSC	BM	BM
Conditioning	BU+FLU+ATG+TBI 200 rads	BU+FLU+ATG	BU+FLU+ATG
GVHD prophylaxis	CY-pós+SIR+MMF	CSP +MTX	CSP+MTX
Post-HCT complications	Acute GVHD in skin and liver (grade II)	Acute skin GVHD, CMV reactivation, SAH	Graft failure/retransplantation
Post-HCT time	4y 4m	4y 11m	5y
Current situation	Alive; 100% donor cells, clinically stable, no immunosuppressants, asthma	Alive; 100% donor cells, no immunosuppressants, bronchiolitis obliterans, asymptomatic AHA pre-BMT	Alive, 100% donor cells, clinically asymptomatic, no immunosuppressants

AHA = autoimmune hemolytic anemia, BMT = bone marrow transplant, BU = busulfan, CMV = cytomegalovirus, CSP = cyclosporine, CTSP PBSC = peripheral blood stem cell, CY = cyclophosphamide, FLU = fludarabine, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplantation, MMF = mycophenolate mofetil, BM = bone marrow, MTX = methotrexate, SAH = systemic arterial hypertension, SIR = sirolimus, TBI = total body irradiation.

Discussion

Although the prevalence of CGD has been estimated at 1 in 200,000 in the United States and Europe^{2,3}, it is still unknown in Brazil. In a series of 71 CGD cases in Latin America (39% Brazilian), Oliveira-Junior et al.⁹ reported a lower rate based on Brazil's population size and international statistics. The present study included 5 patients with CGD, most of them male, with symptom onset in the first year of life but diagnosis around 4 years of age. This is relevant, since CGD leads to serious (and often fatal) infections and/or sequelae in various organs, especially the lungs, early in life. The diagnostic delay may be due to the fact that patients have difficulty accessing professionals who are knowledgeable about the clinical manifestations of inborn errors of immunity, as observed by Dantas et al. when they interviewed physicians about the relevant warning signs.¹²

All patients had respiratory tract infections, some of them with serious clinical manifestations, such as the pleural effusion and fungal pneumonia. The spread of fungal infection to other organs, mainly by *Aspergillus spp.*, has a high mortality rate and is common in patients with CGD.^{2,10} In this study, however, *C. albicans* was the most common species, which may be related to patient characteristics or technical difficulties in isolating other fungi. There were no cases of liver abscess, which are commonly described in patients with CGD.^{2,3} However, *E. coli* and *Enterobacter spp.* were observed, which are uncommon in CGD.

Mycobacterial infection, either by *M. tuberculosis*, which causes tuberculosis, or by *M. bovis*, which can be introduced through the BCG vaccine, is part of the clinical spectrum of CGD in countries where tuberculosis is endemic, as was observed in this study.^{9,11} A severe adverse reaction to the BCG vaccine is also an early clinical manifestation of other inborn errors of immunity, such as severe combined immunodeficiency.^{9,13} In countries where the vaccine is mandatory, such as Brazil, it has a major impact on patient survival. Thus, there have been proposals to postpone applying the vaccine in children until immune disorders have been ruled out.^{9,11,13} The lung abnormalities observed in chest computed tomography generally result from pneumonia cases occurring prior to diagnosis, in addition to a chronic inflammatory process, and can influence patient survival and quality of life.^{2,3} Gastrointestinal manifestations, such as esophageal granuloma, are common, although, unlike other studies, we found no cases of colitis.^{2,3,10}

All patients received prophylaxis with trimethoprim-sulfamethoxazole associated with antifungals, and there were no relevant adverse effects. Prophylaxis with trimethoprim-sulfamethoxazole has been an established practice for more than 40 years and is effective in reducing infections.^{2,3} Since the 1990s, antifungals, especially itraconazole, have been part of the therapeutic arsenal for CGD, considerably reducing deaths due to fungal pneumonia.^{2,14}

Three patients underwent HCT. Brazilian studies on HCT for CGD are still scarce.^{5,6} HCT is indicated for all patients with poorly controlled CGD and for those with significant morbidity, such as recurrent life-threatening infections or progressive lung disease.¹⁴ Among patients with CGD, survival after HCT has increased due to several factors, such as reduced-toxicity conditioning, better cell sources and donor selection, advances in antimicrobial therapy, and younger age at HCT.^{6,14,15} However, the procedure is still considered high-risk and is associated with significant morbidity and mortality, especially for patients under 14 years of age.^{14,15} Two of the transplant patients were teenagers with several comorbidities and a high risk of both short- and long-term complications. They received reduced-toxicity conditioning and the graft was successful. Two had mild graft-versus-host disease, which was controlled with corticosteroids, and they are not immunosuppressed. The other patient developed secondary graft failure, which was successfully resolved with a second transplant. This patient is also alive and has been clinically stable for more than 4 years since transplantation.

Conclusion

Since CGD is a serious disease with onset of symptom in childhood, diagnostic suspicion and early therapeutic intervention can increase survival. Careful monitoring for serious infections and prompt treatment are crucial for long-term survival. Periodic evaluation of pulmonary changes is suggested for all patients. In Brazil, HCT can be considered a viable treatment for patients with CGD, even in late adolescence.

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Effects of social distancing during the COVID-19 pandemic on childhood rhinitis

Efeitos do isolamento social pela pandemia por COVID-19 na rinite infantil

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ABSTRACT

Introduction and objective: The COVID-19 pandemic required children to spend more time at home, and this change had a direct impact on the manifestations of various diseases, including rhinitis. Rhinitis is inflammation of the nasal mucosa caused mainly by exposure to allergens, resulting in symptoms such as rhinorrhea, sneezing, nasal obstruction, conjunctival hyperemia, and itchy eyes and nose. This study aimed to evaluate the consequences of social distancing in children with rhinitis in order to understand the changes in the disease pattern during the pandemic. **Methods:** We conducted a cross-sectional observational study with data obtained through an electronic questionnaire answered by parents and/or guardians of children aged 5 to 12 years. **Results:** From a total of 116 responses, 51.7% of children were male with a median age of 8.5 years. In 81% of cases, rhinitis symptoms improved or remained unchanged during the period of social distancing. In a quarter of the sample, there was a worsening of patients' quality of life. The symptoms with the greatest worsening were sneezing and nasal itching, and the symptom with the greatest improvement was rhinorrhea. The most frequent symptom triggers were pets, carpets, and perfumes. Medication use was reported in 59.4% of cases, with the use of over-the-counter medications in 32.7% of them. **Conclusion:** The results showed that social distancing had a positive impact on the clinical manifestations of rhinitis in the study population.

Keywords: Allergic rhinitis, social distancing, quality of life, pediatrics, child.

Introduction

The novel coronavirus pandemic outbreak in March 2020 led to a period of social isolation and a series of changes in children's routines, as they were required

RESUMO

Introdução e objetivo: Devido à pandemia do novo coronavírus, as crianças passaram a ficar mais tempo em casa, e essa mudança implicou diretamente nas manifestações de diversas doenças, inclusive da rinite. A rinite é a inflamação da mucosa causada, principalmente, por alérgenos, ocasionando sintomas como rinorreia, espirros, obstrução nasal, hiperemia conjuntival, prurido nasal e ocular. O objetivo deste estudo é avaliar as consequências do isolamento social nas crianças com rinite, a fim de compreender a modificação da doença nesse período. **Métodos:** O estudo é observacional transversal, com dados obtidos através de um questionário eletrônico, para pais e/ou responsáveis de crianças entre 5 e 12 anos. **Resultados:** No total de 116 respostas, 51,7% das crianças eram do sexo masculino, e a mediana de idade foi de 8,5 anos. Em relação à rinite, em 81% dos casos foi relatado melhora ou manutenção do quadro durante o período de isolamento social. Em um quarto da amostra houve piora na qualidade de vida dos pacientes. Os sintomas com maior piora foram espirros e prurido nasal, e o sintoma com maior melhora foi a rinorreia. Os desencadeantes de sintomas mais frequentes foram animais domésticos, tapetes e perfumes. O uso de medicamentos foi relatado em 59,4% dos casos, sendo que em 32,7% não houve prescrição médica. **Conclusão:** Os resultados encontrados evidenciaram que o isolamento social teve um impacto positivo em relação às manifestações clínicas da rinite na população estudada.

Descritores: Rinite alérgica, isolamento social, qualidade de vida, pediatria, criança.

to spend more time at home. These changes have had a direct impact on the manifestations of various chronic diseases, such as rhinitis.^{1,2}

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It is known that rhinitis has several subtypes. However, in general, rhinitis is defined as an inflammation of the nasal mucosa caused mainly by contact with allergens. Still, its flares can be triggered by other factors, such as weather changes, contact with respiratory viruses, irritants (strong odors and cigarette smoke), and stress.¹ Symptoms include rhinorrhea, sneezing, nasal obstruction, nasal and ocular itching, and conjunctival hyperemia.^{1,2}

The spread of the novel coronavirus in Brazil has required the adoption of measures to prevent the number of cases from increasing. As a result, social isolation has become part of children's routines. As a result, children who previously spent up to two-thirds of their day at school and doing other activities now only spend their time at home.³

The changes this new scenario represents, either economically, access to health services, or the closure of schools, have directly affected the quality of life of the pediatric population. Children with chronic illnesses have been particularly affected.⁴

In this light, children who spend more time indoors may have more contact with household allergens such as dust mites, pet epithelia, and mold, favoring rhinitis attacks in sensitized individuals. In addition, stress, which was directly related to routine changes, as children were deprived of meeting their peers, going to school, or to the playground, is a contributing factor to worsening the disease.¹ Furthermore, many children with mental disorders had their treatments interrupted due to lockdown, as seen in the UK, where nearly 26% of children with previous mental illnesses had their access to psychological support interrupted during this period. According to a study conducted in Brazil, the anxiety level in children ranged from 19.4% to 21.8%.⁵ These findings suggest poor stress management in children worldwide and in Brazil, which can have a negative effect on other pre-existing illnesses.⁴

In the midst of such an unusual scenario, parents and guardians were observed behaving differently when dealing with chronic diseases such as rhinitis in their children. It is known that this disease, when improperly treated or left untreated, leads to poorer quality of life, with repercussions on children's sleep, school performance and learning, causing irritability and frustration.⁶ Some families are being stricter with their treatment, whether medication or environmental control, as they spend more time at home and are more aware of domestic issues. On the other hand, some families, for fear of the coronavirus, do not seek

pediatric care to assess their child's current situation, thus hindering proper control of the disease.⁴

According to the WHO, "health is a state of complete physical, mental, and social well-being and is not merely the absence of disease or infirmity."⁷ Therefore, it is of the utmost importance to understand what influence the pandemic and, consequently, social isolation have had on the lives of children with chronic illnesses. This study aimed to assess the consequences and compare the symptoms of social isolation in children with any type of rhinitis who spent more time at home exposed to household allergens during the pandemic and, consequently, had fewer upper airway infections.⁴

Methods

This is an observational, cross-sectional study based on data obtained using an electronic questionnaire on the Google Forms platform. The questionnaire included questions the researchers had designed, based on validated questionnaires for the study of rhinitis and quality of life in the pediatric population. It was disseminated on virtual platforms and social groups, and 194 participants responded.

The Ethics Committee approved this study (CAAE 44788921.4.0000.0093. Opinion No. 4.642.694).

The study included 116 parents or guardians of children aged between 5 and 12 years, who had experienced social isolation due to the COVID-19 pandemic and who answered "Yes" to the question "Has a physician or health professional ever diagnosed your child with rhinitis?", indicating to the researchers a strong indication of the presence of rhinitis. We excluded 78 questionnaires whose question was answered "No," making the participant less likely to have been diagnosed with rhinitis.

The questionnaire

The sequence of questions in the study (Figure 1) was based on validated questionnaires for assessing children's quality of life - KIDSCREEN,⁸ and also for assessing the disease: RCAT,⁹ CARATkids,¹⁰ and ISAAC Questionnaire with rhinitis module.¹¹ Although no questionnaire aimed specifically at the 5-12 age group, the authors made adjustments in order to formulate questions that parents could answer, aiming for a clear understanding and greater inclusion of ages.

The form includes an Informed Consent Form (ICF), then 2 sections: the first section asks whether their child has ever been diagnosed with rhinitis. If so, the guardian is referred to section 2, with questions assessing the condition of the disease and their child's quality of life. The aim of the questions was to understand the profile of their children according to age and sex. Also, it aimed to establish a relationship between rhinitis associated with asthma and atopic dermatitis through direct questioning about whether they had been previously diagnosed, since the atopic triad can have a negative influence on disease control.¹² The questionnaire also asked about allergic tests and their results. A series of questions was then asked comparing symptoms before and during social isolation, with the following items: improved, worsened, or remained unchanged. They were asked about 7 symptoms related to allergic rhinoconjunctivitis¹: nasal obstruction, nasal discharge, nasal itching, sneezing, ocular itching, tearing, and conjunctival hyperemia. In addition, they were asked about when they sought medical attention due to rhinitis symptoms and what type of care they received (emergency, teleconsultation, routine), as well as the use of medication (type and quantity compared to the period before social isolation). Regarding quality of life, questions covered 5 different points in relation to the period before social isolation: sleep, diet, involvement in schoolwork, physical activity/play, and stress patterns (irritability, anxiety, sadness, and mood swings). The questionnaire asked about exposure to major household allergens and irritants that could trigger allergic rhinitis symptoms in this sample: dust; cigarette smoke; carpets, curtains, blankets, and winter clothing (wool); pets (dogs, cats, and rodents); air conditioning; mold; pollens (gardens and plants); perfumes, cleaning materials, and clothing and room fresheners.

The criterion used for the final analysis was “worsening of the general pattern of the disease” when at least 3 out of 7 symptoms worsened or 2 of the 7 symptoms worsened, in addition to the need for medical attention for this reason. If the patient showed improvement in at least 3 out of 7 symptoms, this was considered to be an “improvement in the general pattern of the disease.” In cases of a draw: 3 worsened symptoms, 3 improved symptoms and 1 symptom remained unchanged, the need for medical attention because of the rhinitis symptoms was considered: children who needed medical attention were considered to have a “worsened

disease pattern,” those who did not need medical attention were considered to have an “improved disease pattern.” If neither of these criteria were met, they were considered as “disease pattern remained unchanged.”

In addition, “general worsening in quality of life” was considered when their child worsened in at least 2 out of 5 variables mentioned. If there was an improvement in at least 2 out of 5 variables, it was considered to be an “general improvement in quality of life.” In cases of a draw, 2 variables improved, 2 variables worsened, and 1 variable remained unchanged, it was considered to be a “worsening in the overall quality of life.” If none of these criteria were met, “quality of life remained unchanged.”

These data were collected and entered into a Microsoft Excel spreadsheet. The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to assess the normality of the quantitative data using GraphPad Prism 3.0. The quantitative variables were expressed as medians (interquartile range). The chi-square test and Fisher's exact test were used to compare the qualitative data using SPSS 17.0. Continuous variables were compared using the Mann-Whitney non-parametric test. P-values of less than 0.05 were considered statistically significant.

Results

After excluding questionnaires whose respondent answered negatively to the initial question about the diagnosis of rhinitis, 116 out of 194 questionnaires were included in the analysis. The sociodemographic data indicated a slight prevalence of male patients, representing 51.7% ($n = 60$) of the sample. The median age was 8.5 years, interquartile range 6-10. As for the general pattern of rhinitis, when comparing the pattern of the disease in children before the pandemic and during lockdown, 50% improved ($p = 0.002$), about 20% worsened, and around one-third remained unchanged ($p = 0.005$). In terms of quality of life, a grouped analysis was chosen, not looking specifically at sleep, diet, participation in activities, and leisure time. As a result, more than half of these cases remained unchanged, one-quarter reported a worsening, and around 20% improved.

According to the answers provided in the questionnaire, an overall improvement was seen in 57.14% ($n = 4$) of the 7 symptoms assessed, and the remainder remained unchanged (42.86%; $n = 3$)

when compared to the time before the pandemic. Individually, among the ocular symptoms, pruritus was the worst, present in 16 cases (13.8%). The symptom which improved the most was tearing, totaling 45 cases (38.8%), compared to ocular pruritus, which improved in 42 children (36.2%). As for nasal symptoms, nasal obstruction and rhinorrhea improved the most, as reported by 60 and 68 patients, respectively (51.7% and 58.6%). Sneezing and nasal itching were the symptoms that worsened the most in the children, each 21 reports (18.1%) (Table 1). The only item concerning quality of life was stress, analyzed separately. This showed improvement in only 10% of cases (12 children), worsened in 51 children (44%) and remained unchanged in 53 (46%).

As for exposure to symptom-triggering agents during social isolation – such as dust, pets (cats, dogs, rabbits, and other rodents), pollen, mold, perfumes, air conditioning, cigarette smoke, and carpets – the most frequently described were pets (45%), carpets (42%), and perfumes (35%). The least frequently reported irritant was cigarette smoke, only in 1.7% of the cases.

A comparison of the change in rhinitis pattern with the exposed allergens showed that, among children whose rhinitis worsened, the most exposed triggers were carpets and dust, which accounted for more than a half of the sample (63.6% and 54.5%, respectively). In relation to children whose disease pattern remained unchanged, there was greater exposure to perfumes (54.3%) and carpets (48.6%). Among the patients whose rhinitis improved, the most commonly reported exposed agents were domestic animals (50.8%) and dust (33.9%) (Table 2).

A comparison between the data on changes in the general pattern of the disease (worsened, unchanged, and improved) and changes in quality of life (worsened, unchanged, improved) showed that among patients who experienced a deterioration in the disease, more than half of them had an associated deterioration in quality of life (59.9%). Meanwhile, among patients who experienced an improvement in the disease, only 5.1% reported that quality of life worsened minimally. Considering that rhinitis is one of the pillars of the atopic triad - rhinitis, asthma, and dermatitis - we also compared how the general pattern of the disease changed to the presence or absence of the triad, noting that among patients whose rhinitis worsened, 18 (81.8%) reported no atopic triad. Of the patients whose disease pattern improved, 43 (72.9%) had no atopic triad, and 85.7% of the patients who reported

that their rhinitis pattern remained unchanged, also had no atopic triad (Table 3).

In the sample studied, 69 children used medication to control rhinitis symptoms during the pandemic, and 36 of them were under medical follow-up with

Table 1

Description of major symptoms in pediatric patients with allergic rhinitis

	N	%
Sneezing		
Worsened	21	18.1
Unchanged	47	40.5
Improved	48	41.4
Nasal itching		
Worsened	21	18.1
Unchanged	43	37.1
Improved	52	44.8
Eye itching		
Worsened	16	13.8
Unchanged	58	50
Improved	42	36.2
Nasal obstruction		
Worsened	15	12.9
Unchanged	41	35.3
Improved	60	51.7
Conjunctival hyperemia		
Worsened	13	11.2
Unchanged	65	56
Improved	38	32.8
Rhinorrhea		
Worsened	9	7.8
Unchanged	39	33.6
Improved	68	58.6
Lacrimation		
Worsened	4	3.4
Unchanged	67	57.8
Improved	45	38.8

medication guidance before to the pandemic. Thus, 35 used more than 1 class of medication, the most commonly prescribed class was nasal corticosteroids, which accounted for 71% of the sample, and antihistamines (55%). In addition to these, systemic

corticosteroids, decongestants, bronchodilators, antileukotrienes, eye drops, nasal saline solution, and homeopathic or herbal medicines were also reported, while systemic corticosteroids were the least used medication class (Table 4).

Table 2

Data on exposure to allergens and irritants in pediatric patients with allergic rhinitis

	Allergic rhinitis					
	Worsened (n=22)		Unchanged (n=35)		Improved (n=59)	
	N	%	N	%	N	%
Triggering factors						
Dust						
Unchanged	10	45.5	28	80	39	66.1
Had more contact	12	54.5	7	20	20	33.9
Animals						
Unchanged	14	63.6	20	57.1	29	49.2
Had more contact	8	36.4	15	42.9	30	50.8
Pollen						
Unchanged	17	77.3	26	74.3	43	72.9
Had more contact	5	22.7	9	25.7	16	27.1
Mold						
Unchanged	19	86.4	31	88.6	58	98.3
Had more contact	3	13.6	4	11.4	1	1.7
Perfume						
Unchanged	16	72.7	16	45.7	42	72.4
Had more contact	6	27.3	19	54.3	16	27.6
Air conditioning						
Unchanged	19	86.4	28	80	47	81
Had more contact	3	13.6	7	20	11	19
Cigarette smoke						
Unchanged	21	95.5	35	100	58	98.3
Had more contact	1	4.5	0	0	1	1.7
Carpets						
Unchanged	8	36.4	18	51.4	41	69.5
Had more contact	14	63.6	17	48.6	18	30.5

During the pandemic, 32 children (27.5%) required medical care due to the perception of an exacerbation of typical rhinitis symptoms. Of these cases, 2 were teleconsultations, 3 were consultations in pediatric emergency rooms, and the remainder were face-to-face consultations in a pediatrician's office. Of the children who did not need medical care for rhinitis symptoms (72.4%), nearly half took their medication at home.

Discussion

This study found that most participants' rhinitis symptoms improved during social isolation as a result of the COVID-19 pandemic. Although the disease and its triggers are multifactorial, with interrelated characteristics, many conditions justify its manifestations and control over time. As observed in some studies on chronic allergic diseases, these children's recovery may have been due to greater parental control over the environment and proper use of medication.¹³ Another hypothesis, which Gelardi pointed out in a study with adult patients with allergic rhinitis, is that less exposure to certain triggers of

the disease, such as pollen, may have contributed to this outcome,¹⁴ although it should be noted that the pediatric population studied in our municipality is more sensitive to dust mites than to grasses and other pollens.¹⁵

The literature describes a significant decline in the occurrence of respiratory diseases, excluding COVID-19, during social isolation. Not only can this be explained by a lower demand for health services, justifying a lower number of diagnoses, but also a reduction due to the breakdown of the main mechanism of viral and bacterial dissemination, less circulation of people, distancing in closed places, absence of socializing in nurseries and schools, greater care with hand hygiene, and use of protective masks, among others.⁴ Therefore, as airway infection is a trigger for rhinitis,¹ we believe that lower levels of infection have a positive impact on greater rhinitis control, which could explain the findings in this study.

The association between asthma and allergic rhinitis has been widely studied, and many authors consider both to be a spectrum of the same disease, which are interrelated in terms of clinical manifestations and therapeutic approach.¹⁶ According to Brazil's

Table 3

Data on quality of life and presence of the atopic triad in relation to rhinitis pattern in pediatric patients with allergic rhinitis

	Allergic rhinitis						p-value
	Worsened		Unchanged		Improved		
	N	%	N	%	N	%	
Quality of life							
Worsened	13	59.1	13	37.1	3	5.1	< 0.0001
Unchanged	9	40.9	21	60	34	57.6	
Improved	0	—	1	2.9	22	37.3	
Atopic triad							
No	18	81.8	30	85.7	43	72.9	0.34
Yes	4	18.2	5	14.3	16	27.1	

Table 4

Data on the classes of drugs used in pediatric patients with allergic rhinitis

Class	Medication	N	%
Antihistamine		38	55
Nasal corticosteroid		49	71
Association of corticosteroid & nasal antihistamine		0	0
Systemic corticosteroid		2	2.8
Decongestant		3	4.3
Bronchodilator		3	4.3
Saline solution		10	14.4
Eye drops		4	5.7
Homeopathy & herbal medicines		5	7.2
Leukotrienes		3	4.3
Others		3	4.3

Rhinitis Consensus,¹ which includes the guidelines of the ARIA (Allergic Rhinitis and its Impact on Asthma) study, the importance of environmental control on both diseases is reinforced, as is the treatment of these conditions in order to improve patients' quality of life. Ferraro et al.¹³ showed that children with concomitant asthma and allergic rhinitis had no change in symptom control during social isolation, remaining stable. In our study, this sample improved their symptom pattern.

On the other hand, studies with samples of pediatric and adult patients sensitized to allergenic agents such as dust mites have documented a deterioration in the disease pattern during social isolation. This is because, in patients with positive allergic tests for this allergen, staying indoors has become a risk factor for the manifestation of rhinitis.^{17,18} This is difficult to compare with the data in this study, as patients' allergenic sensitization was not documented, but their guardians' reports were. As for the different allergens, it should be noted that although exposure to dust mites occurs indoors and exposure to pollen occurs outdoors, the changes that social isolation imposed have altered families in uneven ways, and

this study did not address the type of residence of the participants.

It could be seen that most children were taking some medication, especially nasal corticosteroids and systemic antiallergic drugs. However, only about one-third of them had a specific consultation to follow up the disease. Our hypothesis for this finding is that patients found it difficult and were afraid to go to a health care service because of the risk of being contaminated with COVID-19.¹ Ferraro also points out that the fear of contamination by SARS-CoV-2 has led to continued use of medication.¹³ There is a high prevalence of children with allergic rhinitis who seek emergency care during asthma exacerbations, but only 2% of the sample required it, indicating better control of both diseases, given that severe asthma is a reason for seeking medical care.²⁰

The sample also reported very low attendance at teleconsultations. This meant that a physician could not follow up on some patients, which favored self-medication during this time, as this is already a common practice in our country and can be harmful to children.²¹

PART 1 - Questions for patient screening.

“Has a physician or health professional ever diagnosed your child with rhinitis?”

- ☐ Yes
☐ No

PART 2 - Only if the respondent answered “Yes” to the question asked in PART 1.

“What is your child’s age? (number only)” (Discursive)

“What is your child’s gender?” (Check 1 item)

- ☐ Female
☐ Male
☐ Other

“What is your relationship with this child?” (Check 1 item)

- ☐ Mother
☐ Father
☐ Brother / sister
☐ Relative or legal guardian

“Has your child ever had any of the following diagnoses? (more than 1 item may be checked)”

- ☐ Asthma
☐ Atopic dermatitis (skin)
☐ I don’t know
☐ Never had these diagnoses

“Has your child ever had an allergy test, either blood or skin?” (Check 1 item)

- ☐ Yes, with a positive result
☐ Yes, with a negative result
☐ Never had an allergy test
☐ I don’t know

From this point on, all the questions will COMPARE how your child used to feel BEFORE the pandemic/social isolation with DURING the pandemic/social isolation, according to your perception as a guardian.

“During the time your child was at home due to the pandemic, the symptom “stuffy nose”.” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
☐ Worsened compared to the time before the pandemic
☐ Remained unchanged

“During the time your child was at home due to the pandemic, the symptom “runny nose”.” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
☐ Worsened compared to the time before the pandemic
☐ Remained unchanged

“During the time your child was at home due to the pandemic, the symptom “itchy nose”.” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
☐ Worsened compared to the time before the pandemic
☐ Remained unchanged

“During the time your child was at home due to the pandemic, the symptom “sneezing”.” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
☐ Worsened compared to the time before the pandemic
☐ Remained unchanged

“During the time your child was at home due to the pandemic, the symptom “itchy eyes”.” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
☐ Worsened compared to the time before the pandemic
☐ Remained unchanged

“During the time your child was at home due to the pandemic, the symptom “tearing/runny eyes”.” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
☐ Worsened compared to the time before the pandemic
☐ Remained unchanged

Figure 1
 Questionnaire for the survey

“During the time your child was at home due to the pandemic, the symptom “red eyes”:” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
- ☐ Worsened compared to the time before the pandemic
- ☐ Remained unchanged

“During the time your child was at home due to the pandemic, their eating habits, due to the symptoms of rhinitis:” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
- ☐ Worsened compared to the time before the pandemic
- ☐ Remained unchanged

“During the time your child was at home due to the pandemic, their sleeping, due to rhinitis symptoms:” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
- ☐ Worsened compared to the time before the pandemic
- ☐ Remained unchanged

“During the time your child was at home due to the pandemic, involvement with schoolwork/classes, due to rhinitis symptoms:” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
- ☐ Worsened compared to the time before the pandemic
- ☐ Remained unchanged

“During the time your child was at home due to the pandemic, the involvement with playing and doing physical activity, due to the symptoms of rhinitis:” (Check 1 item)

- ☐ Improved compared to the time before the pandemic
- ☐ Worsened compared to the time before the pandemic
- ☐ Remained unchanged

“During the time your child was at home due to the pandemic, did you notice a change in stress patterns (irritability, anxiety, sadness, mood swings) due to rhinitis symptoms?” (Check 1 item)

- ☐ I noticed that their stress level increased
- ☐ I noticed that their stress level decreased
- ☐ I noticed that their stress level remained unchanged

“During the time your child was at home due to the pandemic, did they come into greater contact with the following items, compared to the time before the lockdown?” (more than 1 item may be checked)

- ☐ Dust
- ☐ Cigarette smoke
- ☐ Carpets, curtains, blankets, winter clothes (wool)
- ☐ Animals such as cats, dogs, rabbits, and other rodents
- ☐ Air conditioning
- ☐ Mold
- ☐ Grass and plant pollen
- ☐ Perfumes, cleaning materials, room, and clothing fresheners

“During the time your child was at home because of the pandemic, did they need to go to the doctor because of rhinitis?” (Check 1 item)

- ☐ Yes, they went to the emergency hospital (emergency room) because of their rhinitis
- ☐ Yes, they went for a routine non-emergency consultation because of their rhinitis
- ☐ Yes, they had a teleconsultation because of their rhinitis
- ☐ They did not have to see the doctor because of their rhinitis

“During the time your child was at home due to the pandemic, did they need to take medication for their rhinitis?” (Check 1 item)

- ☐ Yes, they took the same amount of rhinitis medication as before the pandemic
- ☐ Yes, but they took more rhinitis medication than before the pandemic
- ☐ Yes, but they took less rhinitis medication than before the pandemic
- ☐ No, they did not take any medication before and did not need to take it

“If your child took any medication, write down which ones they took before and which ones they took during the pandemic to treat their rhinitis.” (Discursive)

Figure 1 (continuation)

Questionnaire for the survey

Another issue that has been widely addressed amid this pandemic is mental health. In this regard, children's stress was assessed, and symptoms including irritability, anxiety, sadness, and mood swings were found to be significantly affected during this time: only 10% of children experienced an improvement in stress, which is in line with other studies.^{13,22,23}

In addition to these issues, questions related to changes in eating habits, sleep, leisure, and school activities due to rhinitis symptoms were grouped together in this study and showed no change compared to the period before social isolation. In general, the study by Chmielik et al.²⁴ on children with rhinitis before the COVID-19 pandemic showed that they already had a poorer quality of life compared to healthy children. These observations cannot be compared with those of healthy children, as our study had no control group.

In terms of sleep, the literature shows moderate evidence of change during social isolation, with more hours, but not necessarily poorer quality of sleep.²⁵⁻²⁷ An Italian study with obese children pointed to an average reduction of 2.5 hours of physical activity per week during the pandemic, indicating long-term metabolic complications and a potential decline in quality of life.²⁸ However, in our study we did not measure the number of hours spent on this activity; we only found that, in their parents' view, children did not change their habits during lockdown due to the symptoms of rhinitis. As for eating habits, changes due to rhinitis symptoms did not affect children's daily routine in our study and the literature is not consistent, since decision-making about the menu is mostly made by guardians, who can either limit access to processed foods and fast food because they are at home, or increase their consumption at home due to stress.²⁶

The main limitation of this study was the inability to have direct contact with the participants, making it impossible to diagnose rhinitis using criteria and physical examination findings at a doctor's consultation. In addition, as this was a cross-sectional study, it was not possible to follow whether, after the period of resumption of social interactions, the pattern of the disease changed or worsened again for most patients, indicating a clearer cause-effect relationship between the periods. It is therefore suggested that more studies be conducted in the pediatric population, prospectively, in order to better clarify these findings.

Conclusion

This study revealed an improved general pattern of rhinitis in children aged between 5 and 12, as per their guardians' perception. We believe that there was less exposure to infectious agents (such as respiratory viruses and bacteria) and non-infectious agents that function as triggers for rhinitis symptoms. It is concluded that social isolation had a positive effect on the disease, as well as on the quality of life of these children.

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Hypogammaglobulinemia and rituximab: case reports

Hipogamaglobulinemia e rituximabe: relato de casos

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ABSTRACT

Secondary immunodeficiency can result from neoplasms, infections, or immunosuppressive therapy. Rituximab (RTX) is an anti-CD20 antibody that depletes B lymphocytes and can induce symptomatic hypogammaglobulinemia. We report 3 cases of symptomatic hypogammaglobulinemia associated with the use of RTX. In patient 1 with rheumatoid arthritis, RTX induced low levels of immunoglobulins and recurrent airway infections. RTX discontinuation led to a normalization of the humoral immune response. Patients 2 and 3, treated with RTX for non-Hodgkin lymphoma and systemic lupus erythematosus, respectively, developed persistent secondary hypogammaglobulinemia requiring immunoglobulin replacement therapy for years. After RTX discontinuation, patients may experience rapid recovery of humoral function or remain with low serum immunoglobulin levels for extended periods. With the increasing use of therapies targeting components of the immune system, a high degree of clinical suspicion for the development of secondary immunodeficiency may minimize the morbidity and mortality associated with these therapies.

Keywords: Rituximab, rheumatoid arthritis, antibiotic prophylaxis.

RESUMO

As imunodeficiências secundárias podem ser uma consequência de neoplasias, infecções ou tratamentos imunossupressores. O rituximabe (RTX) é um anticorpo anti-CD20 que depleta os linfócitos B e pode induzir uma hipogamaglobulinemia sintomática. Aqui, relatamos três casos de hipogamaglobulinemia sintomática associada ao uso de RTX. Na primeira paciente com artrite reumatoide, o RTX induziu a baixos níveis de imunoglobulinas associadas a infecções de vias aéreas de repetição. Após a suspensão do RTX, houve normalização da resposta imune humoral. Os outros dois casos, com o uso de RTX para tratamento de linfoma não-Hodgkin e lúpus eritematoso sistêmico, respectivamente, as pacientes evoluíram com hipogamaglobulinemia secundária persistente, com necessidade de reposição de imunoglobulina por vários anos. Pacientes tratados com RTX podem apresentar, após a sua suspensão, uma recuperação rápida da função humoral ou permanecerem com baixos níveis séricos de imunoglobulinas por longos períodos. Com o crescente uso dos tratamentos direcionados para componentes do sistema imunológico, um alto grau de suspeição clínica para o aparecimento de imunodeficiências secundárias pode minimizar a morbimortalidade associada a estes tratamentos.

Descritores: Rituximab, artrite reumatoide, antibioticoprofilaxia.

Introduction

Immunodeficiencies, conditions that affect correct functioning of the immune system, can be classified as primary, recently renamed as “inborn errors of immunity”, or secondary. Secondary immunodeficiencies can occur due to

underlying diseases, such as neoplasia, infection, or immunosuppressive treatment. Secondary immunodeficiencies are more prevalent than primary immunodeficiencies and often go unrecognized by clinicians.¹

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B lymphocyte disorders are the most common subtype of immunodeficiency, responsible for approximately 50% of diagnosed primary immunodeficiencies. They are characterized by increased susceptibility to bacterial respiratory tract infections, particularly those due to *Streptococcus pneumoniae* and *Haemophilus influenzae*. Symptoms include recurrent sino-pulmonary infections, such as otitis media, sinusitis, and pneumonia. Diarrhea, fatigue, autoimmune manifestations (particularly cytopenia), and hearing loss are also common. Patients with humoral immunodeficiency have decreased or absent serum immunoglobulin levels, but may have normal or increased levels with abnormal function.²⁻⁴

In 1997, rituximab (RTX), an anti-CD20 monoclonal antibody, was the first antibody to be approved for relapsed or refractory CD20+ follicular or low-grade B-cell non-Hodgkin lymphoma. Its use was then extended to other B-cell malignancies and to non-malignant diseases such as rheumatoid arthritis. Using RTX to deplete B lymphocytes in patients with rheumatoid arthritis, either as monotherapy or in association with cyclophosphamide and/or corticosteroids, has been part of the therapeutic arsenal since 1998.³

The binding of RTX to CD20 may result in B lymphocyte apoptosis through mechanisms that are not yet fully understood. RTX binding can also activate the classic complement pathway, resulting in membrane attack complex and cell lysis. Additionally, it recruits natural killer cells by binding to FcγRII, which leads to antibody-mediated cellular cytotoxicity and,

finally, macrophages phagocytose the target cell by recognizing RTX- bound CD20.³ After RTX treatment, around 38.5% of patients have low IgG levels, and sino-pulmonary infections occur in an average of 6.6%. Immunoglobulin replacement appears to reduce the frequency of infections.⁴ Although the depletion of immunoglobulin M (IgM) after RTX treatment is more frequent and prolonged than that of IgG, it is less clinically significant.⁵ Here, we present and discuss 3 cases of hypogammaglobulinemia associated with RTX treatment in the context of lymphoma or autoimmune disorders.

Presentation of the cases

Case 1

V.F.P.D., a 47-year-old woman, has been diagnosed with rheumatoid arthritis for 11 years. After several therapeutic regimens with little response, RTX was initiated, which led to symptom control. Six months after initiating RTX, the patient began experiencing recurrent acute sinusitis, a total of 5 episodes in the last 12 months, with subsequent chronification and recurrent pneumonia (5 episodes during the same period) (Table 1). She reported 2 hospitalizations in the last month, in which intravenous broad-spectrum antibiotics (meropenem) were used to treat pneumonia. Computed tomography of the paranasal sinuses (Figure 1A and 1B) and chest (Figure 2A and 2B) performed between infections showed pansinus involvement and bronchiectasis, respectively. She did not present with lower respiratory symptoms;

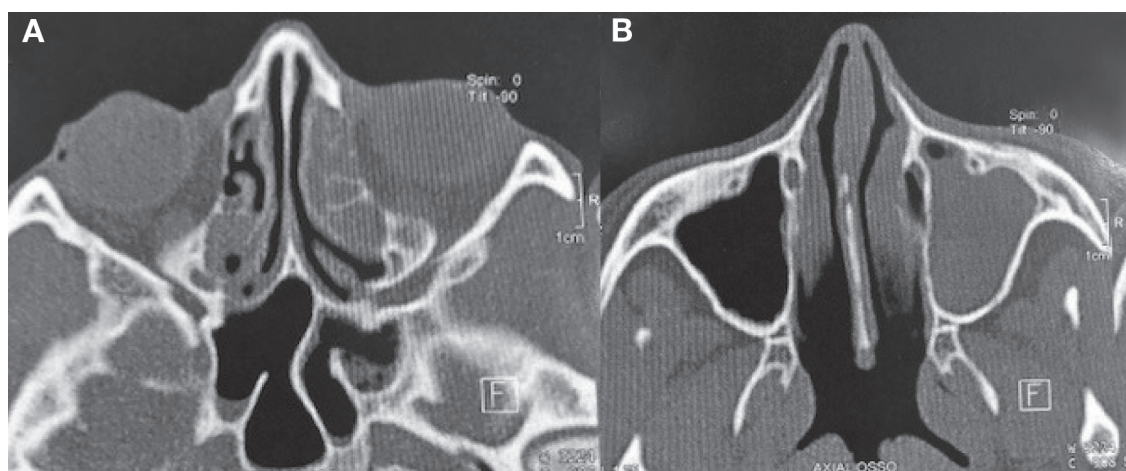


Figure 1

Computed tomography of the paranasal sinuses. Axial section showing diffuse haziness of ethmoid cells and the right maxillary sinus, as well as secretion in the sphenoid sinuses

pulmonary auscultation showed no changes, although a moderate amount of bilateral mucopurulent rhinorrhea was observed in the initial assessment.

Regarding family history, she has a maternal aunt diagnosed with rheumatoid arthritis. The laboratory test results (reference values [RV] for age) were: IgM: 25 mg/dL (RV: 33–293), IgG: 593 mg/dL (RV: 739–1390), IgA: 129 mg/dL (RV: 65–421), IgE: 46.2 kU/L (≤ 140 kU/L), serum protein electrophoresis: gamma globulin 8.8%-0.55 g/dL (10.3%-18.2%, 0.74-1.75 g/dL)(Table 2); other routine tests were normal.

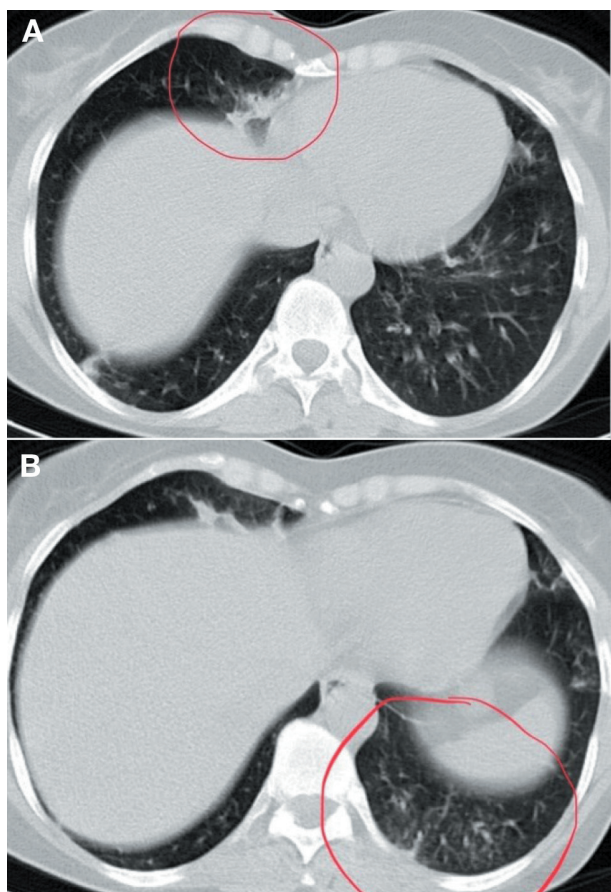
Immunophenotyping of lymphocyte subpopulations showed a lack of B lymphocytes (CD19) and $< 1\%$ of peripheral blood lymphocytes; other cell types were normal (see Table 3). Once hypogammaglobulinemia secondary to RTX treatment was diagnosed, prophylactic antibiotic therapy with sulfamethoxazole/trimethoprim was initiated at 800/160 mg twice a day, and intravenous human immunoglobulin (IVIG) replacement was indicated. IVIG was prescribed at an immunomodulatory dose by the attending rheumatologist: 2 g/kg of weight for the first application.

Table 1

Clinical course of the cases

	Sex/ Age	Previous diagnosis	Chemo- immuno- therapy	Time of RTX use until ID diagnosed	Sym- ptoms	Serum IgG level in ID diagnosis	Treatment, etc.	Current serum IgG level
Case 1	♀, 47 years	Rheumatoid arthritis	RTX	6 months	Acute sinusitis and recurrent PNM	593 mg/dL (RV 739- 1390 mg/dL)	RTX suspended. Tofacitinib prescribed. IVIG: 2 g/kg every 28 days, being suspended 10 months later. ATB: SMX/TMP	1025 mg/dL (RV 739- 1390 mg/dL) 3 months after start
Case 2	♀, 32 years	Systemic lupus erythematosus	RTX	3 years	Sinusitis, acute otitis and recurrent PNM	698 mg/dL (RV 739- 1390 mg/dL)	RTX suspended. HQC + MTX prescribed IGIV: 400 mg/kg every 28 days ATB: SMX/TMP	855 mg/dL (RV 739- 1390 mg/dL)
Case 3	♀, 48 years	Non-Hodgkin lymphoma	RTX	1 year	Sinusitis, acute otitis, and recurrent PNM	623 mg/dL (RV 952- 1538 mg/dL)	RTX suspended. IGIV: 416 mg/kg every 28 days	1112 mg/dL (RV 739- 1390 mg/dL) 5 months after start

ATB = antibiotic, HQC = hydroxychloroquine, ID = immunodeficiency, IgG = Immunoglobulin G, IGIV = intravenous immunoglobulin, PNM = pneumonia, RTX = rituximab, RV = reference value, SMX = sulfamethoxazole, TMT = trimethoprim.

**Figure 2**

Chest computed tomography showing bronchiectasis in the lingula and mucus stasis in peripheral bronchioles

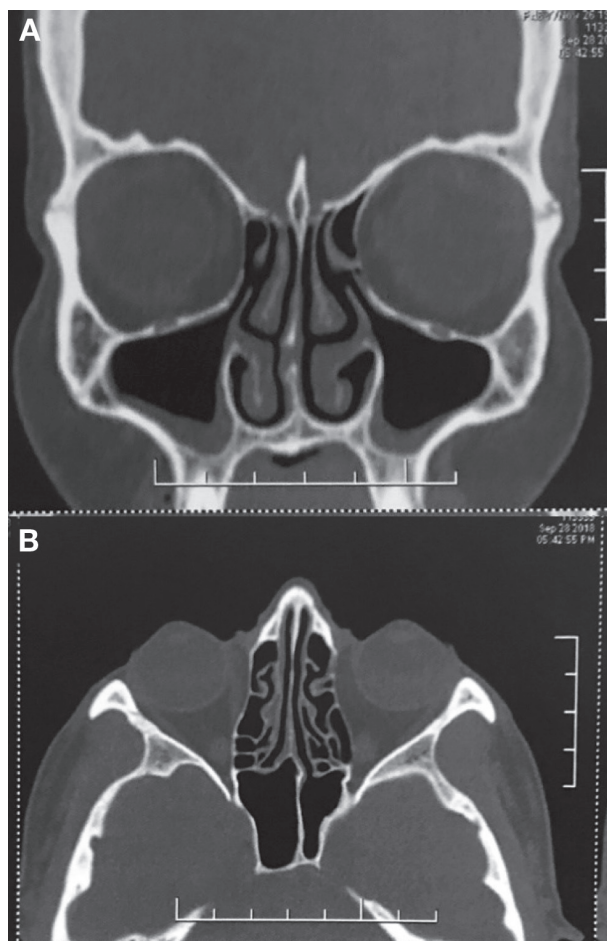
The rheumatologist preferred to suspend RTX and prescribe tofacitinib. Approximately 3 months after the initial consultation and 1 month after RTX had been suspended and IVIG therapy had begun, total serum IgG (1025 mg/dL) normalized. Since then (> 10 months of follow-up), the patient has had no further infectious conditions. Her rheumatoid arthritis remains controlled and antibiotic prophylaxis with sulfamethoxazole/trimethoprim was suspended after serum IgG levels normalized (Table 2). Radiological findings indicated normalized sinuses and improved lung condition (Figures 3A and 3B).

Case 2

J.T.V., a 48-year-old woman with non-Hodgkin lymphoma, was treated with chemotherapy and RTX in 2012. About a year after using RTX, she began having recurrent infections, including several pneumonias, otitis, and sinusitis, requiring antibiotic

therapy (Table 1). Tomography of the facial sinuses showed pansinus mucosal thickening (Figure 4A and 4B). In December 2018, she was referred to the immunology service, where she was diagnosed with hypogammaglobulinemia (Table 2).

Laboratory tests performed that month showed IgA: < 6.4 mg/dL (RV 153-359 mg/dL), IgE: < 4.3 mg/dL (RV < 100 mg/dL), IgG: 623 mg/dL (RV 952-1538 mg/dL), and IgM: 17.5 mg/dL (RV 73-171 mg/dL). Immunophenotyping of lymphocyte subpopulations revealed a lack of B lymphocytes (Table 3). Serology for pneumococci from January 2019: serotype 4: < 0.5, serotype 6b: < 0.5, serotype 9v: < 0.5, serotype 14: 3.4, serotype 18c: < 0.5, serotype 19f: 1.2, and serotype 23f: < 0.5.

**Figure 3**

Computed tomography of the paranasal sinuses 6 months after the first exam (Figure 1) showing normalization of the sinus disease. Mild non-specific thickening of the mucus persists on the maxillary sinus floor

Table 2
Serial immunoglobulin dosage

	Serum IgG level at ID diagnosis	Serum IgG level at follow-up	Current serum IgG level
Case 1	593 mg/dL (RV 739-1390 mg/dL)	–	1025 mg/dL (RV 739-1390 mg/dL)
Case 2	698 mg/dL (RV 739-1390 mg/dL)	798 mg/dL (RV 739-1390 mg/dL)	855 mg/dL (RV 739-1390 mg/dL)
Case 3	623 mg/dL (RV 952-1538 mg/dL)	564 mg/dL (RV 952-1538 mg/dL)	1112 mg/dL (RV 739-1390 mg/dL)

ID = immunodeficiency, IgG = Immunoglobulin G, RV = reference value.

Immunoglobulin measurements were repeated in February 2019, showing IgG: 623 mg/dL, IgE: < 4.3 mg/dL, IgM: < 17.5 mg/dL, and IgA: < 6.4 mg/dL; immunophenotyping confirmed a lack of B cells (Table 3). In May 2019, due to symptomatic hypogammaglobulinemia and the lack of B cells,

IVIg was initiated at a dose of 25 g (416 mg/kg) every 28 days, after which the patient presented no further symptoms or infections and required no antibiotic therapy. A new immunoglobulin dose was administered in July 2019 (ie, 2 months after starting IVIg), with the following results: IgE: < 2 mg/dL, IgA:

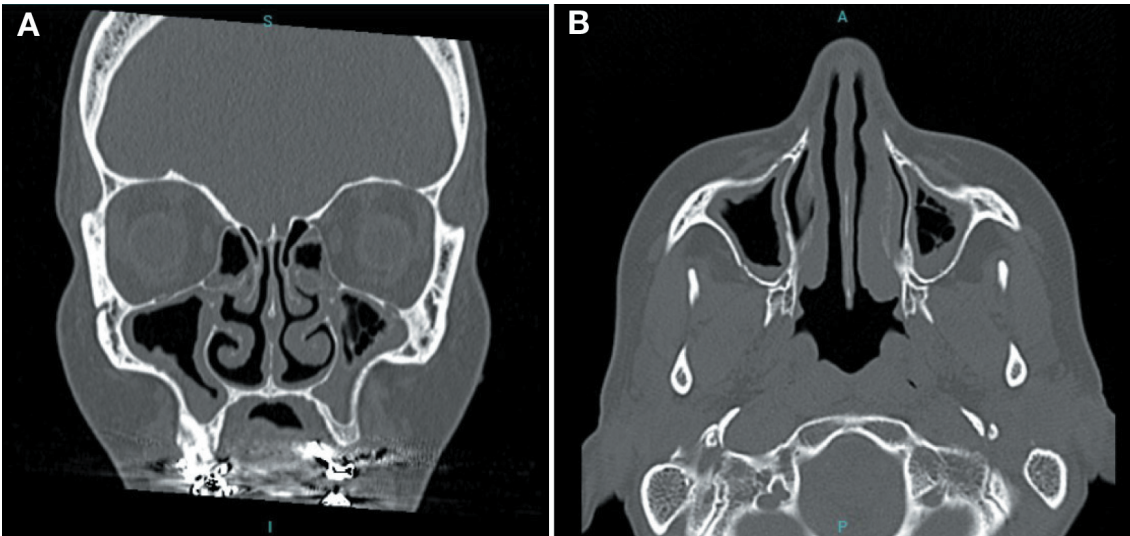


Figure 4
Computed tomography of facial sinuses from September 2014 (coronal and axial sections) demonstrating bilateral thickening of the mucus and some ethmoid cells

< 10 mg/dL, IgG: 1112 mg/dL, and IgM: < 20 mg/dL. Since the B lymphocyte deficiency in peripheral blood persisted in new immunophenotyping (Table 3) in January 2020, immunoglobulin replacement with IVIG was continued at the same dose, pending further follow-up.

Case 3

P.R.V.F., a 32-year-old woman, was initially diagnosed with relapsing polychondritis approximately 10 years ago and was treated with methotrexate and prednisone. Three years later, due to oral and esophageal ulcers, polychondritis of the small and

Table 3

Serial immunophenotyping of peripheral blood lymphocytes

	Case 1	Case 2	Case 3
Immunophenotyping at diagnosis	CD3: 1959 cells/mm ³ (RV 100-3900 cells/mm ³) CD19: 2 mm ³ cells/mm ³ (RV 90-680 cells/mm ³) CD4: 1126 cells/mm ³ (RV 560-2700 cells/mm ³) CD8: 1047 cells/mm ³ (RV 211-724 cells/mm ³) CD56: 320 cells/mm ³ (RV 87-760 cells/mm ³) CD4/CD8: 1.26 cells/mm ³ (RV 1.2-4.5 cells/mm ³)	CD3: 2393 cells/mm ³ (RV 849.1-1963.3 cells/mm ³) CD19: 54 cells/mm ³ (RV 124.2-415.9 cells/mm ³) CD3/CD4: 1479 cells/mm ³ (RV 477.5-1140.8 cells/mm ³) CD3/CD8: 860 cells/mm ³ (RV 211.7-724.6 cells/mm ³) CD56: 134 cells/mm ³ (RV 137-567.8 cells/mm ³) CD4/CD8: 1.71 cells/mm ³ (RV 1.2-4.5 cells/mm ³)	CD3: 1238 cells/mm ³ (RV 849.1-1963.3 cells/mm ³) CD19: 0 cells/mm ³ (RV 124.2-415.9 cells/mm ³) CD3/CD4: 411 cells/mm ³ (477.5-1140.8 cells/mm ³) CD3/CD8: 602 cells/mm ³ (RV 211.7-724.6 cells/mm ³) CD56: 29 cells/mm ³ (RV 137-567.8 cells/mm ³) CD4/CD8: 0.68 cells/mm ³ (RV 1.2-4.5 cells/mm ³)
Immunophenotyping after suspending rituximab	–	CD3: 1458 cells/mm ³ (RV 849.1-1963.3 cells/mm ³) CD19: 281 cells/mm ³ (RV 124.2-415.9 cells/mm ³) CD3/CD4: 689.1 cells/mm ³ (RV 477.5-1140.8 cells/mm ³) CD3/CD8: 726 cells/mm ³ (RV 211.7-724.6 cells/mm ³) CD56: 86 cells/mm ³ (RV 137-567.8 cells/mm ³) CD4/CD8: 0.94 cells/mm ³ (RV 1.2-4.5 cells/mm ³)	CD3: 1192 cells/mm ³ (RV 849.1-1963.3 cells/mm ³) CD19: 54 cells/mm ³ (RV 124.2-415.9 cells/mm ³) CD3/CD4: 331 cells/mm ³ (RV 477.5-1140.8 cells/mm ³) CD3/CD8: 783 cells/mm ³ (RV 211.7-724.6 cells/mm ³) CD56: 55 cells/mm ³ (RV 137-567.8 cells/mm ³) CD4/CD8: 0.42 cells/mm ³ (RV 1.2-4.5 cells/mm ³)

RV = reference value.

large joints and malar erythema, associated with laboratory changes, such as increased C-reactive protein and positivity for antinuclear factor and anti-DNA antibodies, she was diagnosed with systemic erythematosus lupus. After tocilizumab therapy failed, RTX was introduced, leading to significant symptomatic improvement after 3 months.

The patient began experiencing severe recurrent respiratory infections approximately 3 years after RTX treatment began, one of which required admission to intensive care for sepsis secondary to sinusitis. Over the next 4 years, she experienced 25 episodes of sinusitis and 2 episodes of pneumonia (Table 1). Laboratory tests performed approximately 3 years after RTX treatment began showed B lymphocyte depletion, as well as hypogammaglobulinemia (Tables 2 and 3): IgG: 698 mg/dL (RV: 739-1390), IgA: 57 mg/dL (RV: 65-421), and IgM: 22 mg/dL (RV: 33-293; CD20 B lymphocytes: 54 cells/mm³ (90-680 mm³). At that point it was decided to suspend RTX and switch to hydroxychloroquine associated with methotrexate. After 2 years of sustained infections, antibiotic prophylaxis was begun with sulfamethoxazole/trimethoprim, which did not prevent new infections. IVIG replacement was then initiated at a dose of 400 mg/kg every 28 days. Six months after the first dose of IVIG, suspension was attempted, but her immunoglobulin levels continued to decline progressively, despite normalization of B lymphocytes. IVIG replacement was restarted at the previous dose and common variable immunodeficiency was suspected.

Discussion

In this case report, we evaluated 3 women in the third or fourth decade of life, 2 of whom had autoimmune diseases (rheumatoid arthritis [Case 1] and systemic lupus erythematosus [Case 3]), and the other had a neoplasm (non-Hodgkin lymphoma [Case 2]).

At some point in their treatment, all 3 patients used RTX, a chimeric anti-CD20 monoclonal antibody. This medication depletes B lymphocytes, but only 38.5% of patients present hypogammaglobulinemia and approximately 6.6% present symptomatic hypogammaglobulinemia⁵, which is clinically expressed as recurrent sino-pulmonary infection. Despite recurrence, these common infections are caused by typical germs. Thus, diagnosis of secondary

symptomatic hypogammaglobulinemia may be late, ie, when the patients already have sequelae, such as bronchiectasis, as in Case 1. To avoid such complications, a high degree of clinical suspicion is necessary. Symptomatic hypogammaglobulinemia occurred in all 3 patients. After the diagnosis, IVIG replacement therapy was performed (at an immunomodulatory dose in Case 1 and a replacement dose in Cases 2 and 3).

In Case 1, to avoid treatment with 2 high-cost medications, the rheumatologist replaced RTX with a different therapeutic regimen to control the underlying rheumatoid arthritis. In this case, IgG levels normalized after RTX was suspended and the therapeutic regimen was changed. The patient had no new infections by the end of follow-up. This patient was monitored in a private practice and lived in a distant city. Furthermore, at one point her health insurance lapsed, which made it impossible to carry out laboratory tests. Similar impediments to testing occurred in Cases 2 and 3, who were monitored in a public health unit.

In Case 3, after suspending RTX, the immunoglobulin levels did not normalize and the patient had an autoimmune disease, so a diagnosis of common variable immunodeficiency was suggested. Common variable immunodeficiency is the most common primary immunodeficiency in adults. B lymphocyte dysfunction leads to low serum IgG levels and, usually, IgA and/or IgM. As a consequence, patients can develop recurrent bacterial airway infections (often later in life). Other clinical disorders have been widely described, such as chronic enteropathy, malignant or benign lymphoproliferative diseases, granulomatous diseases, and autoimmune disorders.⁶⁻⁸ Thus, although the recurrent respiratory infections may have been due to common variable immunodeficiency rather than RTX treatment, the patients continue with IVIG replacement and no longer suffer them. Although recurrent infection is the main presentation of primary immunodeficiency, autoimmunity is also a factor, often due to loss of self-tolerance.⁹

In the Case 2, due to persistent hypogammaglobulinemia, IVIG replacement continued for several years after suspending RTX treatment for non-Hodgkin lymphoma. Barmettler et al. classify patients with post-RTX hypogammaglobulinemia into 2 subgroups: (1) normal immunoglobulin and B lymphocyte recovery, and (2) persistent symptomatic hypogammaglobulinemia. In the latter group, there is an increased risk of infection due to humoral dysfunction/deficiency and these patients may benefit

from IVIG replacement.⁶ Case 2 probably belongs to this group.

Case 1 probably belongs to the first subgroup due to the rapid recovery of immunoglobulin and B lymphocyte levels, whereas Case 2 may belong to the persistent hypogammaglobulinemia subgroup. The average duration of IVIG replacement therapy in the persistent hypogammaglobulinemia subgroup is 83 months after RTX is suspended, compared to an average of 24 months in the normal recovery subgroup.⁶ This is why in Case 3, even though other immunoglobulin classes decreased, common variable immunodeficiency still could not be diagnosed conclusively. It can be challenging to distinguish patients with sustained hypogammaglobulinemia from those with primary immunodeficiencies, especially common variable immunodeficiency.¹⁰

Conclusions

In these 3 cases, the patients developed humoral immunodeficiency, which, if not diagnosed in time, can have severe clinical repercussions. In Cases 1 and 3, there was a significant delay between the onset and diagnosis of humoral immunodeficiency syndrome. In Case 1, the pulmonary sequelae proved irreversible even after adequate treatment. With the development of new monoclonal antibodies for a wide variety of diseases, especially in patients who use anti-B lymphocyte antibodies, a high degree of clinical suspicion is necessary regarding symptomatic secondary hypogammaglobulinemia, initiating antibiotic prophylaxis and, if necessary, immunoglobulin replacement therapy.

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Oral mite anaphylaxis (pancake syndrome) in Peru: an underestimated problem?

Anafilaxia por ingestão de ácaros (Síndrome da panqueca) no Peru: um problema subestimado?

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ABSTRACT

Urticaria and angioedema are known to have different etiologies, as they can be allergic, infectious, autoimmune, or spontaneous in nature. In single or recurrent episodes, a hidden triggering allergen should be considered, such as house dust mites (HDMs). Several reports have demonstrated that flours contaminated with HDMs can cause urticaria and angioedema, including severe life-threatening allergic reactions when ingested in large quantities from stored wheat flour. In this study, we report the clinical findings in 31 patients, including cases of anaphylaxis after the ingestion of mite-contaminated flour. We also found a relationship between a clinical history of hypersensitivity to nonsteroidal anti-inflammatory drugs and oral mite anaphylaxis syndrome in atopic patients, consistent with the theory of a “new aspirin triad,” as previously published, and now being described for the first time in Peru.

Keywords: Urticaria, angioedema, mites, anaphylaxis, flour.

RESUMO

Sabe-se que a urticária e o angioedema apresentam diferentes etiologias, pois podem ser de natureza alérgica, infecciosa, autoimune ou espontânea. Em episódios únicos ou recorrentes, deve-se considerar um alérgeno desencadeante oculto, como os ácaros de poeira doméstica (APDs). Vários relatos demonstraram que farinhas contaminadas com APDs podem causar urticária e angioedema, incluindo reações alérgicas graves com risco de vida quando ingeridos em grandes quantidades provenientes de farinha de trigo armazenada. Neste estudo, relatamos os achados clínicos de 31 pacientes, incluindo casos de anafilaxia após ingestão de farinha contaminada com ácaros. Também encontramos uma relação entre uma história clínica de hipersensibilidade a anti-inflamatórios não esteroides e síndrome de anafilaxia por ingestão de ácaros em pacientes atópicos, consistente com a teoria de uma “nova tríade do ácido acetilsalicílico”, conforme publicado anteriormente, e agora sendo descrito pela primeira vez no Peru.

Descritores: Urticária, angioedema, ácaros, anafilaxia, farinha.

Introduction

Urticaria, angioedema, and anaphylaxis can have different etiologies. These may include an allergic reaction, infections, and auto-immunity. If the trigger cannot be identified, these conditions are commonly

designated as idiopathic or spontaneous. In certain cases, a specific cause can be identified, including foods, venoms, or medications. However, in other cases the trigger is not easily recognized.

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When these diseases occur sporadically or as recurrent episodes, a hidden allergenic trigger such as mites should be considered in the investigation process.

A number of reports in the literature have shown that flours contaminated with mites can cause severe life-threatening allergic reactions and anaphylaxis if a patient ingests huge numbers of mites in these stored wheat flours.¹⁻⁴ The first report of systemic anaphylaxis after ingestion of food contaminated by storage mites was published in 1996 by Matsumoto et al.⁵

Methods

In the present study, we report clinical findings from 31 patients, including cases of urticaria, angioedema, and anaphylaxis occurring after ingestion of mite-infested flour. To the best of our knowledge, this is the first time that anaphylaxis caused by ingestion of mite-contaminated flour has been reported in Peru.

Results

The first patient was a 31-year-old man who had recurrent episodes of urticaria. He had a clinical history of rhinitis and hypersensitivity reactions to NSAIDs. He mentioned experiencing two episodes of anaphylaxis 10 years earlier after eating a pancake at home, for which he received treatment at the emergency department of a different medical service. On that occasion, he was treated at the emergency department of another hospital and we do not have access to any more information. While he was being treated for allergic rhinitis at our service (with intranasal corticosteroids), he presented two additional episodes of urticaria within two months; this time the diagnosis of anaphylaxis was not considered. On both occasions he had eaten spaghetti prepared with a white sauce containing mite-contaminated wheat flour.

Based on these findings, we started investigations to clarify the etiology of this recurrent urticaria, working from the hypothesis that the patient might have suffered from the Pancake Syndrome. The Pancake Syndrome, also known as “oral mite anaphylaxis”, is a new syndrome characterized by severe allergic manifestations occurring in atopic patients shortly after intake of foods made with mite-contaminated wheat flour.^{6,7}

The flour used to prepare the white sauce was examined by light microscopy and live mites were

detected (Figure 1). The wheat flour sample was sent to Inmunotek, Spain, to quantify and identify the mite species present in the flour. More than 300 *Tyrophagus putrescentiae* (Acaridae family) mites were present per gram of flour sample.

The patient was skin prick tested (SPT) with standardized allergenic extracts (Hollister Stier, Spokane WA, USA) from the house dust mites *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis* and whole wheat flour (IPI-ASAC, Sao Paulo, Brazil). The tests were read at 15 minutes and wheals with a diameter >3 mm greater than negative control were considered positive. Negative (50% glycerinated HSA-saline) and positive (histamine 10 mg/mL) controls were also tested. The SPT was positive for all 3 mite species and negative for the whole wheat flour extract. This patient tolerated all foods, including those made with uncontaminated wheat flour, without experiencing any reactions.

We concluded that the patient had a systemic reaction caused by ingestion of flour contaminated with *T. putrescentiae* mites. Since flour packages must be stored in a refrigerator to prevent mite



Figure 1

Mites in the wheat flour from the first case (*Tyrophagus putrescentiae*)

contamination and proliferation, we advised our mite-sensitive patient to store wheat flour products in his refrigerator. Since then, no more episodes of recurrent urticaria have occurred.

After this first case was diagnosed, we started a program to investigate patients evaluated at our clinic due to allergic symptoms after eating foods prepared with wheat flour. The objective of this study was to

investigate whether these patients might meet the criteria for diagnosis of Pancake Syndrome. From January 2016 to January 2017, we identified 30 cases with a high degree of suspicion (Table 1). This number represents about 2.2% of the total number of patients evaluated at the emergency room of our institution over this period. In 16 cases we could not obtain the offending flour samples, and, therefore, the diagnosis could not be fully ascertained.

Table 1

Patients in whom pancake syndrome was suspected

Patient	Age (years)	Mites in the flour	HDM SPT	Confirmed diagnosis
I	32	Positive	Positive	Positive
II	13	Positive	Positive	Positive
III	42	Positive	Positive	Positive
IV	16	NA	Positive	NC
V	22	NA	Positive	NC
VI	24	NA	Positive	NC
VII	30	Positive	Positive	Positive
VIII	41	Positive	Positive	Positive
IX	5	Positive	Positive	Positive
X	14	Positive	Positive	Positive
XI	9	NA	Positive	NC
XII	33	NA	Positive	NC
XIII	5	Positive	Positive	Positive
XIV	19	NA	Positive	NC
XV	12	NA	Positive	NC
XVI	11	NA	Positive	NC
XVII	23	Negative	Positive	Negative
XVIII	47	NA	Positive	NC
XIX	23	NA	ND	NC
XX	37	Positive	Positive	Positive
XXI	19	Negative	ND	Negative
XXII	13	NA	Positive	NC
XXIII	33	Positive	Positive	Positive
XXIV	44	NA	Positive	NC
XXV	27	Positive	Positive	Positive
XXVI	41	NA	Positive	NC
XXVII	12	NA	Positive	NC
XXVIII	19	NA	Positive	NC
XXIX	25	Positive	Positive	Positive
XXX	10	NA	Negative	Negative

HDM = house dust mites, SPT= skin prick test, NA = not available, NC = not confirmed.

Studies of the 14 flour samples that were obtained revealed that 12 (85.7%) flour samples contained mites. Microscopic examination using stereoscopes revealed presence of live mites in all the positive samples. In two cases we could not find any mites in the samples examined. However, the absence of live mites cannot rule out the presence of mite allergens. Since mite allergens were not quantified, the absence of these data could represent a weakness of the present study.

Skin prick tests were performed on these patients for house dust mites (Der p and Der f) and whole wheat flour using the same method as described above. The results showed sensitization to both mites in all the patients, suggesting a high degree of mite sensitivity. The tests for whole wheat flour sensitivity were negative and all the patients continued eating foods prepared with uncontaminated wheat flour without experiencing any reactions. These patients and/or their parents were also advised to keep flour in the refrigerator after opening the package.

Discussion

Some reports have demonstrated presence of house dust and storage mites in high altitude areas of South America, including Peru and Ecuador.⁸⁻¹³ These findings differ significantly from studies conducted in Europe, in which very low levels of mites and mite allergens are detected.

The best conditions to allow mite proliferation are relative humidity higher than 70%, mean temperature >25°C, and darkness. In our cases, we observed that flour packages had been stored for a few weeks and some of them for more than 3 months, including beyond expiry dates, in conditions that were optimal for mite proliferation. This fact is important, since it has been shown that there is a direct correlation between the duration of storage of the flour package and the number of mites.¹⁴

In vitro cross-reactivity among house dust and/or storage mites could also explain the sensitization of these patients from Lima to house dust and storage mites and their clinical symptoms.

Some mite proteins are thermostable and may induce symptoms after ingestion, even after cooking, as in cakes, pancakes, or white sauces. Der p2, a major mite allergen, is a thermostable protein, which can resist high temperatures and continue to provoke symptoms after exposure to high temperatures.¹⁵

Therefore, as previously suggested, this allergen may be the culprit responsible for these reactions.

Another relevant finding of this study is confirmation of the relationship between a clinical history of hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) and the OMA syndrome. There are several reports in the literature of sensitivity to aspirin and other NSAIDs, manifested as urticaria or angioedema, in patients with OMA. In 1997, Blanco et al. showed that up to 87% of patients affected with the Pancake Syndrome were sensitive to Aspirin.⁶

Our first patient has the same co-morbidity; allergy to NSAIDs and oral mite anaphylaxis (OMA). There were seven patients allergic to NSAIDs (54%) among the 13 positive Pancake Syndrome cases, one of whom was allergic to acetaminophen. The results shown in Table 2 do not include the first case described above because he was not part of the group of patients evaluated during the period from 2016 to 2017.

Considering that sensitivity to NSAIDs is responsible for 21-25% of reported adverse drug events in the general population¹⁶ and 37% of patients with chronic spontaneous urticaria,¹⁷ the results observed in this and other studies suggest that patients allergic to NSAIDs are at a higher risk of suffering OMA than non-allergic patients. Sensitization to mites and NSAIDs seems to be a significant risk factor. Patients living in tropical and subtropical areas and suffering from these conditions should be advised to keep flour packages in their refrigerators.

Although the mechanism underlying this relationship between atopic patients who had oral mite allergic reactions and hypersensitivity to NSAIDs is unknown, some pathogenic pathways have been suggested and a “new aspirin triad” of allergic rhinoconjunctivitis, aspirin/NSAID hypersensitivity, and severe systemic reactions to mite-contaminated foods has been proposed.¹⁸

In conclusion, this is the first description of the Pancake Syndrome in Peru. Mite sensitized patients suffering from urticaria, angioedema, and anaphylaxis may experience these conditions after ingestion of foods contaminated with mites. Patients allergic to NSAIDs seem to be at a greater risk.

With this study, we hope to raise physicians' awareness about this condition, in order to prevent further life-threatening reactions. We acknowledge that this study has limitations, such as the absence of some flour samples for investigation. Some of the

Table 2

Relationship between pancake syndrome and hypersensitivity to nonsteroid anti-inflammatory drugs (NSAIDs)

Patient	Age (years)	NSAID hypersensitivity	Mites in the flour	SPT with house dust mite extracts	Confirmed diagnosis
I	32	+	+	+	+
II	13	Negative	+	+	+
III	42	+	+	+	+
VII	30	+	+	+	+
VIII	41	Negative	+	+	+
IX	5	Negative	+	+	+
X	14	Negative	+	+	+
XIII	5	Negative	+	+	+
XX	37	+	+	+	+
XXIII	33	+	+	+	+
XXV	27	+	+	+	+
XXIX	25	Negative	+	+	+

+ = positive, NSAID= nonsteroidal anti-inflammatory drug, SPT= skin prick test.

samples used in the cooking process were finished or had been discarded and thus no more samples were available. Based on this preliminary information, greater effort should be made in Peru, and Latin America in general, to disseminate the information available and avoid more severe life-threatening reactions due to ingestion of mite-contaminated flours. The worldwide information currently available about the OMA syndrome should be disseminated to reduce the number of patients affected by this syndrome.

Acknowledgment

We would like to thank Dr. Luciano Poletti and Dr. Eduardo Luna for their input in the Anglola. Special thanks are due to our late friend Mario Sanchez-Borges, who made great contributions to this paper. He participated in the field research, in the processing, and in revision, until he went to a better place. We hope he is looking down on us.

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Pigmented cosmetic contact dermatitis

Dermatite de contato pigmentada por cosmético

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ABSTRACT

Pigmented contact dermatitis is a rare condition associated with numerous cosmetic and textile allergens. It predominantly affects middle-aged women with high phototypes. The patch test is essential to identify the causative agent. Treatment includes removal of the causative agent, sunscreen use, administration of topical bleaching agents, and occasionally abrasive dermatologic procedures. We report a case of pigmented cosmetic contact dermatitis motivated by its clinical exuberance and satisfactory outcome, emphasizing the importance of diagnostic suspicion and adequate management impacting this outcome.

Keywords: Contact dermatitis, pigmentation, cosmetics.

RESUMO

A dermatite de contato pigmentada se destaca por sua raridade, sendo associada a inúmeros alérgenos cosméticos e têxteis. Acomete predominantemente mulheres de meia idade e fototipos altos. O teste de contato é imprescindível para a identificação do agente causal. O tratamento indicado consiste no afastamento do agente causal, no uso de fotoprotetores, clareadores tópicos e, por vezes, procedimentos dermatológicos abrasivos. Relatamos um caso de dermatite de contato pigmentada por cosmético motivado pela exuberância clínica e desfecho satisfatório, ressaltando a importância da suspeição diagnóstica e do manejo adequado impactando neste desfecho.

Descritores: Dermatite de contato, pigmentação, cosméticos.

Introduction

Pigmented contact dermatitis (PCD) is a rare condition characterized by brownish-gray pigmentation on the skin due to melanin deposition, predominantly affecting the face, being more intense on the forehead and temples.¹ The term PCD was coined in the 1970s by Osmundsen and Pinôl Aguadé et al., but Riehl had already described cases of facial hyperpigmentation in 1917 during World War I.² We report a case of PCD to a cosmetic product with an exuberant clinical presentation and a favorable outcome, highlighting the impact of diagnostic suspicion and adequate management on the outcome.

Case report

A 56-year-old woman with Fitzpatrick skin type IV presented with a complaint of “facial patches” for the past 2 years. On examination, there were brownish-gray reticulated patches distributed across the entire patient’s face (Figure 1). The lesions were asymptomatic and had an abrupt onset following the use of a skin-lightening cream (Renovare Accolade®). The patient’s medical history included 4 pregnancies, menopause at the age of 40 (without hormonal replacement therapy), and a previous history of facial melasma after the last pregnancy. Serological tests for hepatitis B and C and antinuclear antibodies were negative, and iron levels were within the normal

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range. Homogentisic acid levels in urine were also normal. An incisional biopsy was performed on the right cheek, revealing epidermal atrophy with foci of basal layer vacuolization, exocytosis of lymphocytes, and keratinocyte apoptosis. The dermis showed solar elastosis, mild superficial perivascular lymphomononuclear infiltration with numerous melanophages, and no signs of ochronosis or hair follicle inflammation. Histopathological findings suggested superficial perivascular dermatitis with significant pigment dispersion (Figure 2). A patch test was performed and yielded a 2+ reaction to the currently used skin-lightening cream and a 1+ reaction to paraphenylenediamine (mix) and 0.5% methyldibromo glutaronitrile. Based on clinical and histopathological findings, the diagnosis of PCD to cosmetics was established. Treatment was initiated with 0.05% clobetasol cream applied to the face at night from Monday to Friday, preceded 30 minutes by a formulation containing 2% hydroquinone cream and 6% glycolic acid, together with sunscreen (SPF 70) during the day. There was gradual improvement in the lesions, with mild reticulated patches remaining on the face after 3 months of treatment, and complete resolution of the condition after 1 year (Figure 3).



Figure 1
Brownish-gray reticulated patches distributed across the patient's face.

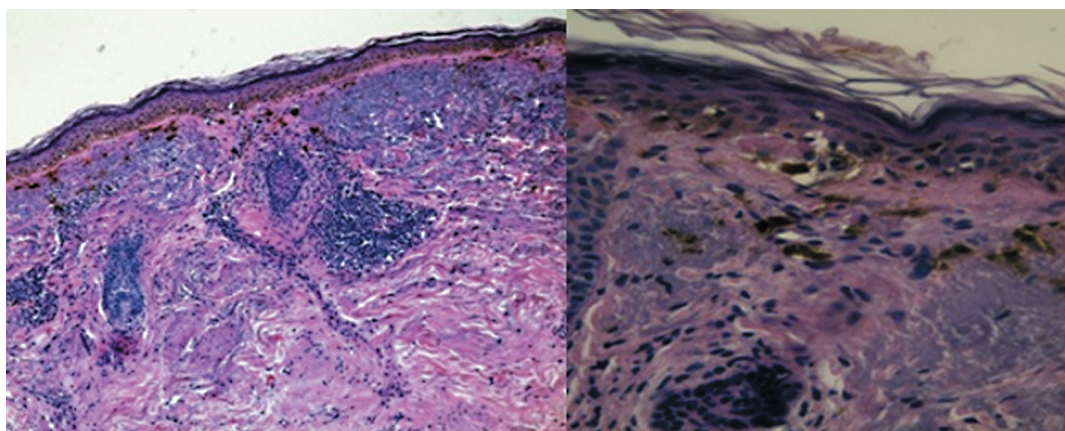


Figure 2
Epidermis: flat. Dermis: superficial perivascular lymphomononuclear infiltration, melanophages, and solar elastosis (H&E 40X). Detail: foci of basal layer vacuolization and keratinocyte apoptosis (H&E 400X).

**Figura 3**

(A) Results after 3 months of treatment, (B) Results after 1 year of treatment

Discussion

PCD is a cutaneous manifestation caused by allergens found in cosmetics and textiles, predominantly affecting middle-aged women with higher Fitzpatrick skin types,² as observed in our patient. Cosmetic allergens include red and yellow pigments, aniline, chromium hydroxide, bactericidal agents (carbanilides, linoleic acid), and hair dyes. Textile allergens include optical brighteners, dyes, textile finishes, mercury compounds, formaldehyde, and rubber components.³ The incidence of PCD is not well-documented, with a significant proportion of cases reported in Japan.⁴ Hyperpigmentation in PCD is believed to be caused by frequent and repeated contact with small amounts of sensitizing allergens.⁵ According to Nakayama et al., allergen concentrations in commercial products are too low to produce typical eczematous dermatitis, but repeated contact with these substances produces a type IV cytolytic reaction characterized by vacuolar degeneration of the basal cell layer and pigment incontinence on histopathology.⁴ Since most cases occur in patients with higher Fitzpatrick skin types, interactions between pigmentation and genetics may be involved in the development of this condition. Clinically, PCD is characterized by diffuse and irregular brownish-gray pigmentation on the face, sometimes preceded by mild erythema (often imperceptible in dark skin) and pruritus. Clinical differential diagnoses include melasma, exogenous ochronosis, and

pigmented lichen planus.^{6,7} A patch test is essential for a definitive diagnosis and identifying the causative agent. It should be performed using both the standard and cosmetic series, including the patient's personal care products whenever possible, as was done in this case. Treatment involves discontinuing the causative agent and using sunscreens, skin-lightening agents (hydroquinone, azelaic acid, kojic acid, and glycolic acid), retinoids, topical corticosteroids, and procedures such as chemical peels, dermabrasion, microneedling, among others,⁷ although results are not always satisfactory.

In conclusion, PCD is a condition that is difficult to diagnose, particularly when the temporal correlation with allergen exposure is not well-established. In suspected cases, patch testing is a crucial tool for reaching a definitive diagnosis and identifying the causative agent, making it a cornerstone of PCD treatment.

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Sensitization to poultry meat, fish, and coconut in a multiple food allergic young boy

Sensibilização a carne de aves, peixe e coco em um jovem com alergia alimentar múltipla

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ABSTRACT

Poultry meat allergy is rare and may present as primary or secondary, in the context of bird-egg syndrome. Chicken meat is responsible for most of the reactions. Cross-reactive allergens (parvalbumins, enolases, aldolases) between fish and chicken meat have been described. Coconut allergy is also rare. Coc n2 (7S globulin) and Coc n4 (11S globulin) have been implicated. We present a complex multiple food allergy case report where investigation into fish and chicken meat allergies as well as coconut allergy is carried out.

Keywords: Food hypersensitivity, foods containing coconut, fish proteins, immunoblotting, poultry proteins.

RESUMO

A alergia à carne de aves é rara e pode apresentar-se como primária ou secundária, no contexto da síndrome ovo-ave. A carne de frango é responsável pela maioria das reações. Foram descritos alérgenos com reação cruzada (parvalbuminas, enolases, aldolases) entre peixe e carne de frango. A alergia ao coco também é rara. Coc n2 (globulina 7S) e Coc n4 (globulina 11S) foram implicados. Apresentamos um relato de caso complexo de alergia alimentar múltipla, onde é realizada investigação sobre alergia a peixe e carne de frango, bem como alergia ao coco.

Descritores: Hipersensibilidade alimentar, alimentos de coco, proteína de peixe, imunoblotting, proteína de aves domésticas.

Introduction

Poultry meat allergy is rare and may present as primary or secondary, in the context of bird-egg syndrome. Chicken meat is responsible for most reactions.^{1,2} A new clinical syndrome has recently been described involving cross-reacting allergens between fish and chicken meat (fish-chicken syndrome), mainly parvalbumin.²⁻⁴ Coconut allergy is also rare, although it has been increasing in the last few years due to the widespread use of coconut oil and milk in cooking and skin care products. Coc n 1 (7S globulin) and Coc n 4 (11S globulin) have been described as its main allergens.^{5,6}

Case report

We report the case of a 16-year-old boy, referred to us for consultation because of multiple food allergy. Symptoms started when the boy was 8-10 years old after fish ingestion (abdominal pain, vomiting, oropharyngeal pruritus, facial erythema, and lip angioedema), first with salmon and then with codfish, horse mackerel, sea bass, and canned tuna.

At the age of 15, the patient started to present multiple other food reactions. He experienced several anaphylactic reactions to poultry meat, first with chicken meat and then with turkey and duck meat, characterized by facial pruritus, lip angioedema,

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laryngeal tightness, abdominal pain, and diarrhea. He had always tolerated hen's eggs. However, he had been exposed to domestic birds from 2-3 and from 11-12 years of age and there were pigeon lofts at the back of his house. Furthermore, he developed tongue angioedema and oropharyngeal pruritus after cashew, pistachio, and hazelnut ingestion, although he tolerated almonds and peanuts. He also complained of oral allergy syndrome after ingestion of unpeeled peach. The most recent reaction happened after ingestion of a coconut cake, when he experienced lip angioedema and facial pruritus. Interestingly, the patient had used body cream and shampoo containing coconut oil for the previous 4-5 years. He had a personal history of mild persistent rhinitis, but no history of atopic eczema.

Skin-prick tests (SPT) and prick-prick tests (PPT) were positive for all fishes tested, except for tuna and monkfish (fresh and cooked), with a specific IgE value (sIgE) (ImmunoCAP, Phadia) for parvalbumin (rGad c 1) of 0.64 kU/L (Table 1). Poultry meat (chicken, turkey, and duck meat) allergy was also confirmed with SPT and PPT, with sIgE for chicken meat of 4.28 kU/L. Curiously, he had positive PPT for fresh and cooked egg yolk/white. SPT and sIgE were positive for cashew, pistachio, and hazelnut. PPT was positive for peach skin (negative for pulp) with sIgE for peach 0.39kU/L and sIgE for rPru p 3

and rPru p 7 < 0.35 kU/L. Coconut sensitization was also confirmed with PPT and sIgE (3.5 kU/L). Immuno Solid-phase Allergen Chip (ISAC) results showed very high levels of serum specific IgE to rDer p 2 and rDer f 2, moderate/high levels to rDer p 1, rDer f 1, rDer p 10, nPen m 1, rAni s 3 and nBla g 7, and low levels to rGad c 1, rCor a 8 and Fel d 1, with negative values for nGal d 5 and rPru p 3 (Table 1). Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) IgE immunoblotting assays were performed to better understand coconut sensitization and whether poultry meat allergy could have emerged in the context of fish-chicken syndrome.

Protein extracts from fresh coconut and coconut water were prepared by homogenization in phosphate buffered saline (20% W/V) (50 mM phosphate buffer, 100 mM NaCl, pH 7.5) with magnetic stirring, centrifugation to remove the non-soluble materials, dialysis of the supernatants against distilled water, and lyophilization.

SDS-PAGE IgE-immunoblotting revealed intense IgE binding bands at 24 kDa, 22 kDa, and 16.5/15.5 kDa in both coconut extracts, and a pair of bands at 55 kDa and 40 kDa were only detected in the fresh coconut extract (Figure 1). Comparing the molecular mass of these bands with those described for the coconut allergens,⁷ we assume that the patient is probably sensitized to coconut 7S globulin (Coc n 1),

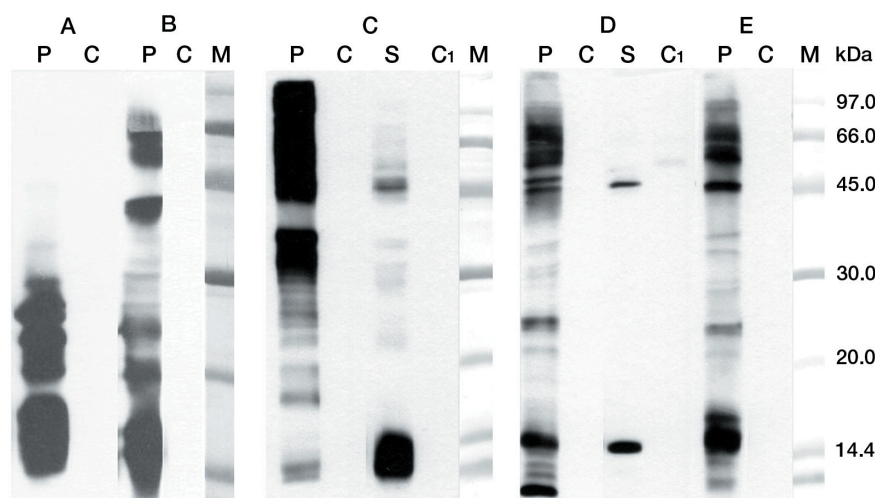


Figure 1

SDS-PAGE IgE-Immunoblotting. (A) Coconut water extract, (B) Fresh coconut extract, (C) Cod extract, (D) Chicken thigh extract, (E) Chicken breast extract. Lane P: Patient serum, Lane C: Control serum (pool of sera from non-atopic subjects), Lane S: Rabbit serum against sardine parvalbumin, Lane C1: Unimmunized rabbit serum, Lane M: Molecular mass standard.

Table 1

Skin-prick tests with aeroallergens, food extracts and food allergens, culprit food prick-prick tests, and specific IgE levels evaluated by ImmunoCAP and ISAC

	SPT ^a (mm)	PPT ^a (mm)	sIgE (kU/L) ^b	ISAC (ISU-E)
Aeroallergens				
<i>D. pteronyssinus</i>	13	–	54.2	rDer p 1: 11 rDer p 2: 26 rDer p 10: 11
<i>D. farinae</i>	10	–	39.8	nDer f 1: 1.3 nDer f 2: 19
<i>Blomia tropicalis</i>	4	–	–	–
<i>Euroglyphus maynei</i>	14	–	–	–
<i>Lepidoglyphus destructor</i>	6	–	3.45	–
<i>Cat epithelium</i>	5	–	3.22	rFel d 1: 0.3
Foods and food allergens				
Peach	–	Peel: 8 Pulp: 0	0.39	–
Nectarine	–	Peel: 8 Pulp: 0	–	–
rPru p 3	11	–	<0.35	
rPru p 4	–	–	<0.35	
rPru p 7	–	–	<0.35	
Almond	0	0	<0.35	–
Hazelnut	6	–	1.3	rCor a 8: 1.1
Pistachio	26	–	1.5	–
Cashew	19	–	0.69	–
Walnut	0	5	0.97	–
Peanut	0	5	<0.35	–
Coconut	–	8	3.5	–
Chicken meat	8	–	4.27	–
Turkey meat	10	–	0.71	–
Duck meat	–	Fresh: 12 Baked: 11	–	–
Egg yolk	0	Fresh: 5 Baked: 6	–	–
Egg white	0	Fresh: 10 Baked: 5	–	–
Ovomucoid	0	–	–	–
Ovalbumin	0	–	–	–
Parvalbumin	–	–	0.64	rGad c 1: 0.4
Codfish	12	–	–	–
Salmon	6	–	1.26	–
Sole	5	–	0.73	–
Sardine	7	–	0.65	–
Tuna ^c	0	Canned tuna: 4	–	–
<i>Anisakis</i>	–	–	0.61	rAni s 3: 3.7
Other tropomyosins:				nBla g 7: 7.8 nPen m 1: 6.4

^a Mean papule diameter (mm). Histamine: 6mm.

^b Total IgE: 563 kU/L.

^c Other fishes tested: Hake (fresh: 6mm, baked: 11mm), Catfish (fresh: 22mm, baked: 16mm), Grouper (fresh: 10mm, baked: 10mm), Swordfish (fresh: 15mm, baked: 15mm), Plaice (fresh: 10mm, baked: 7mm), Horse mackerel (fresh: 7mm, baked: 22mm), Flat fish (fresh: 10mm, baked: 5mm), Corvina (fresh: 7mm, baked: 9mm), Gilt-head sea bream (fresh: 13mm, baked: 9mm), Baita (fresh: 5mm, baked: 7mm), Sea bass (fresh: 5mm, baked: 9mm), Trout (fresh: 14mm, baked: 15mm), Salmon trout (fresh: 18mm, baked 10mm), Beetle (fresh: 10mm, baked: 16mm).

ISAC = Immuno Solid-phase Allergen Chip; SPT = Skin-prick test; PPT = Prick-prick test; sIgE = Specific IgE antibody levels.

while the bands at approximately 55 kDa lead us to suppose that light sensitization to 11S globulin (Coc n 4) could be involved in this case.

Protein extracts from raw cod and chicken (thigh and breast) were prepared as mentioned above. SDS-PAGE immunoblotting revealed IgE reactivity at 60, 52, 45, 39, 31, 20, 18, and <14 kDa in cod extract and several IgE-bands between 85-45 kDa, and bands at 25, 16, and <14 kDa in chicken extracts (Figure 1). A rabbit serum against sardine parvalbumin detected bands with the same molecular weight to some of the bands detected in chicken (16 kDa) and cod extracts (< 14 kDa). This result suggests the patient could be sensitized to fish beta-parvalbumin and chicken alpha-parvalbumin. SDS-PAGE IgE immunoblotting-inhibition using raw chicken and cod extracts in the solid phase did not show any significant cross-reactivity between chicken and cod proteins (Figure 2).

Conclusion

Primary sensitization to poultry meat is even less common than bird-egg syndrome.^{1,8} Alpha-parvalbumin and myosin light chain 1, enolase and aldolase are relevant allergens that have been implicated in primary poultry meat sensitization and also in cross-reactivity with fish.^{1,2,9} Negative nGal d 5 values allow exclusion of bird-egg syndrome. The low specific IgE detected against fish parvalbumin and the IgE-reactive bands appearing at around 60 – 40 kDa in cod extract blots let us to suppose fish enolase or aldolase could be implicated in this case. Interestingly, our patient presented an asymptomatic co-sensitization to egg white/yolk. Hemmer et al. also found positive sIgE values (>0.35 kU/L) for egg yolk and/or white in 66% of poultry meat allergic patients, although these values were much lower than those for chicken meat.¹ However, the causal link remains unclear.

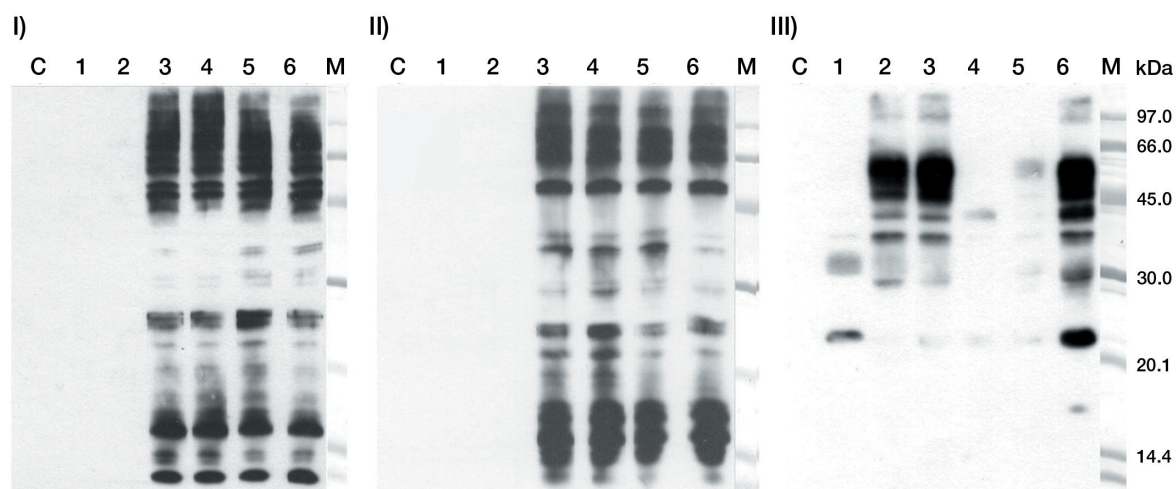


Figure 2

SDS-PAGE IgE-Immunoblotting-inhibition. I) Solid phase: Chicken thigh extract; II) Solid phase: Chicken breast extract. Lane C: Control serum (pool of sera from non-atopic subjects) Lanes 1 – 6: Patient serum pre-incubated with chicken thigh extract (lane 1), with chicken breast extract (lane 2), with hake extract (lane 3), with cod extract (lane 4), with salmon extract (lane 5), with sunflower pollen extract (lane 6), Lane M. Molecular mass standard. III) Solid phase: Salmon extract. Lane C: Control serum (pool of sera from non-atopic subjects) Lanes 1 – 6: Patient serum pre-incubated with cod extract (lane 1), with chicken thigh extract (lane 2), with chicken breast extract (lane 3), with hake extract (lane 4), with salmon extract (lane 5), with sunflower pollen extract (lane 6), Lane M. Molecular mass standard.

Coconut sensitization does not seem to be more likely in peanut or tree nut sensitized patients.¹⁰ However, cross reactivity with walnuts and hazelnuts has been reported.¹⁰ Our patient presents co-sensitization to coconut and peanut/tree nuts but different protein families seem to be involved.

We report an interesting case of multiple food allergy with primary sensitization to poultry meat, fish, and coconut. The patient currently tolerates several fishes (sole, plaice, corvina, golden, baila, tuna, and monkfish) and has been doing elimination of poultry meat, coconut, peanut, and tree nuts without any additional food reaction.

Acknowledgments

The authors are grateful to Roxall for their help with the investigation.

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Baker's rhinitis and asthma with concomitant wheat anaphylaxis: a rare overlap of clinical entities

Rinite e asma do padeiro com anafilaxia após ingestão de trigo: um caso raro de sobreposição de entidades clínicas

Filipa Rodrigues-dos-Santos¹, Inês Falcão¹, Borja Bartolome², Leonor Cunha¹

ABSTRACT

Wheat is one of the fundamental sources of food worldwide. Baker's asthma and occupational rhinitis are both frequent and can be attributable to work exposure in bakers. However, the association between baker's asthma and wheat allergy is very rare. The authors report the case of a bakery worker who developed baker's asthma and occupational rhinitis after years of working in a bakery and later developed anaphylactic reactions after wheat ingestion.

Keywords: Occupational asthma, rhinitis, anaphylaxis, food hypersensitivity.

RESUMO

O trigo é uma das fontes alimentares mais importantes em todo o mundo. A asma do padeiro e a rinite ocupacional são frequentes e podem ser atribuídas à exposição a farinhas em padeiros. No entanto, a associação entre asma do padeiro e alergia alimentar ao trigo é muito rara. Os autores descrevem um caso em que um trabalhador de panificação desenvolveu asma do padeiro e rinite ocupacional após anos trabalhando em uma padaria, e posteriormente desenvolveu reações anafiláticas após a ingestão de trigo.

Descritores: Asma ocupacional, rinite, anafilaxia, hipersensibilidade alimentar.

Introduction

Wheat (*Triticum aestivum*) is one of the fundamental sources of food worldwide.¹ Depending on the route of exposure, wheat is responsible for different clinical manifestations of IgE-mediated allergy.² Ingestion of wheat can induce food allergy or wheat-dependent exercise-induced anaphylaxis; inhalation of wheat and rye flour is the main cause of baker's asthma.

Baker's asthma is a frequent form of occupational asthma, and affects up to 15% of bakers, millers, and pastry workers.³ Inhalation of cereal flour proteins

triggers an IgE-mediated bronchial reaction and can also result in rhinoconjunctivitis and contact urticaria.³

Proteins constitute approximately 10-15% of wheat grain and can be classified into two different fractions: salt-soluble proteins (albumins and globulins) and salt-insoluble proteins (prolamins, namely gliadins and glutenins).^{4,5} Salt-soluble proteins, including alpha-amylase inhibitors, peroxidase, thioredoxin, nonspecific lipid transfer proteins (LTPs), serine

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protease inhibitor, and thaumatin-like protein (TLP), are known allergens associated with Baker's asthma.^{4,5}

Each of these fractions contains allergens that may induce a clinical reaction, although there is no consensus definition on either major or minor allergens, nor on their allergenicity after heating and processing.¹ Wheat flour LTPs (Tri a 14) have recently been identified as important allergens linked to both Baker's asthma and IgE-mediated food allergy.^{4,5} Omega-5 gliadin (Tri a 19), associated with wheat-dependent exercise-induced anaphylaxis (WDEIA), has been associated with wheat food allergy.³

Recent studies in the United States in children and adults with wheat food allergy show a prevalence of about 0.5% in children and 0.8% in adults, with 50% being of adult-onset.⁶ Although the association of Baker's asthma with wheat food allergy is very rare, overlapping between these two clinical entities may be possible through allergens such as alpha-amylase inhibitors, LTPs, and gliadins due to their sensitization potential through inhalation. Rarely, patients may develop symptoms after eating meals contaminated with uncooked wheat flour, but otherwise they do not report problems after ingestion of cooked wheat.⁶

Clinical case

The patient was a 45-year-old woman, resident in Porto, with a personal history of seronegative generalized myasthenia gravis, without any medication or other significant medical or surgical history. She worked as a counter attendant in a bakery shop for over two decades. Initially, she was asymptomatic, but after approximately 20 years she developed persistent symptoms of watery rhinorrhea, nasal itching, and nasal obstruction. She also experienced occasional wheezing and dyspnea after contact with flour in the workplace. She remained asymptomatic during holiday periods.

Two years after the onset of respiratory symptoms, the patient had 2 episodes of generalized maculopapular rash, with associated symptoms of pruritus, dyspnea, and throat tightness, approximately 15 minutes after ingestion of wheat bread. She had no history of infection, no drug or alcohol intake, or exercise prior to the episode. She presented at the Emergency Department and was treated with IM adrenaline 0.5mg/0.5ml, methylprednisolone 1 mg/kg IV, and clemastine 2g IV. Her serum tryptase level was

10.7 µg/L (reference value <10 µg/L) four hours after onset of symptoms, compared to 3.67 µg/L, obtained after the episode was resolved.

She was referred to the Immunology and Allergy clinic for further study. Skin prick tests were conducted for common inhalants and flours, which were positive (mm) for oat extract 6.5; rye extract 9, wheat extract 9, and histamine 9. The patient had a total IgE level of 100 kU/L. Specific IgE was positive (kUA/L) for wheat extract 11.20, rye extract 9.53, oat extract 0.77, and gluten 11.40, and negative for corn extract 0.21, rTri a 19 0.01 and rTri a 14 0.06. Spirometry findings were within the normal range. The post-bronchodilation test (with salbutamol) was negative. A bronchial provocation test with methacholine was positive. An open oral wheat provocation test was not performed due to the history of anaphylaxis. A bronchial provocation test with wheat flour was not performed due to the history of anaphylaxis. The ImmunoCAP™ ISAC test was negative.

SDS-PAGE Immunoblotting

Protein and Allergenic Profile

In order to study the IgE-binding protein profile, SDS-PAGE immunoblotting was performed in non-reducing conditions (without 2-mercaptoethanol). The patient's serum was incubated with gluten and extract from wheat seed and whole wheat flour. The IgE binding detected was much higher for the extracts of wheat seed and whole wheat flour than for the gluten sample. The wheat seeds and whole wheat flour extracts showed similar IgE binding profiles. Among others, two bands at approximately 15.5 kDa and 13 kDa were detected (Figure 1).

Based on her clinical history and the results of additional studies, the patient was diagnosed with occupational rhinitis, baker's asthma, and wheat-induced food allergy with anaphylaxis. An adrenaline autoinjector (Epipen® 0.3mg/0.3ml) was prescribed as well as desloratadine 5mg sos and prednisolone 60mg sos. A Mandatory Occupational Disease Report was submitted to the Portuguese Department of Protection against Occupational Risks, and a 100% work disability was assigned for a bakery work post. The patient underwent job reassignment with avoidance of inhalation of and contact with the cereal involved. Since then, she remains asymptomatic and maintains elimination of wheat ingestion, inhalation, and contact.

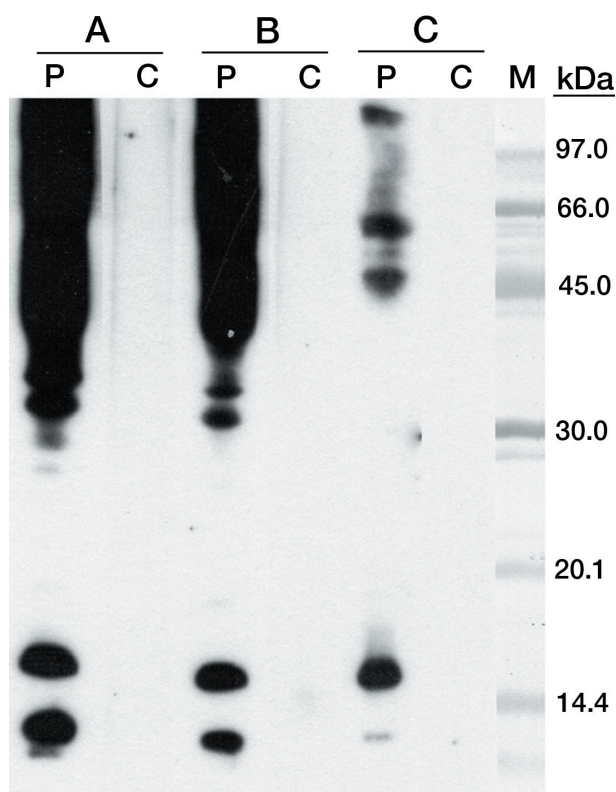


Figure 1
SDS-PAGE Immunoblotting

A) Wheat seed extract; B) Whole wheat flour extract; C) Gluten sample; Lane P = patient serum; Lane C = control serum; Lane M = Molecular mass marker.

Discussion

Food allergy to wheat in adults is a rare IgE-mediated hypersensitivity reaction, unlike baker's asthma, which is considered a significant occupational disease among bakery workers.¹ Most patients with baker's asthma do not show a concomitant food allergy. Bakers with occupational asthma typically consume bread and other foods containing wheat flour without developing adverse reactions. Our case is of particular interest, with an IgE-mediated mechanism being demonstrated both for baker's asthma and food allergy in the same patient.

In this case, sIgE to wheat proteins were detected in the patient's serum, which might be responsible for an allergic reaction upon exposure to, contact with, or ingestion of wheat. The IgE-binding band at approximately 15.5 kDa detected with wheat seed and whole wheat flour extracts has the same molecular

weight as Tri a 30, described in the literature;⁷ and the IgE-binding band of approximately 13 kDa detected in these same extracts has the same molecular weight as Tri a 28.⁷

The World Health Organization (WHO) allergen database lists 27 allergens for wheat, but the clinical relevance of many of them remains undetermined.⁸ Tri a 28 and Tri a 30 are alpha-amylase/trypsin inhibitors and are members of the prolamin superfamily, one of the most allergenic proteins found in wheat. Wheat prolamins share sequence and structural homology with each other and with other proteins in rye and barley,⁹ highlighting the importance of investigating cross-reactivity in this case. Alpha-amylase inhibitors have been associated with both baker's allergy and food allergy,⁹⁻¹¹ which is also described in our case.

Tri a 19 is by far the best characterized wheat allergen and is a major allergen for wheat-dependent exercise-induced anaphylaxis. It is also an important allergen in baker's asthma. However our patient seems not to be sensitized to Tri a 19. Other clinically relevant allergens include wheat Tri a 14, which has also been associated with baker's asthma¹² and food allergy.¹³ Here we described an IgE-mediated allergy that is probably related to allergens other than Tri a 19 and Tri a 14.

In adults, food allergy to ingested wheat is uncommon and is normally observed as the WDEIA variant, in which symptoms of food allergy appear in response to a combination of wheat ingestion and physical exercise.¹⁴ Moreover, most patients presenting with baker's asthma do not show concomitant wheat food allergy. In this case, we present a rare combination of baker's asthma and wheat-induced anaphylaxis after ingestion of wheat. We emphasize the need for referral of such patients to the Immunology and Allergy clinic, since identification of the causal allergen(s) has potential implications for accurate diagnosis and management of occupational exposition of these patients, with health and legal implications.

Management of IgE-mediated wheat allergy is mainly based on elimination of wheat from the diet and restriction of exposure to wheat flours is recommended in the case of baker's asthma¹⁵ In case of accidental exposure and anaphylactic reaction, an epinephrine auto-injector can be a lifesaving treatment and therefore must be prescribed for all patients with anaphylactic history.

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Regression of dupilumab-induced nasal polyps

Regressão da polipose nasal induzida pelo dupilumabe

Raísa Borges de Castro¹, Diderot Rodrigues Parreira², Pedro Giavina-Bianchi¹

ABSTRACT

We report the case of a patient with chronic rhinosinusitis with nasal polyps treated with dupilumab. The clinical features and impact on the patient's quality of life are described. Computed tomography shows improvement of the inflammatory process and regression of the nasal polyps.

Keywords: Immunobiologic agent, chronic rhinosinusitis with nasal polyps, monoclonal antibody, interleukin-4, interleukin-13, dupilumab.

RESUMO

Relato de caso de paciente com rinossinusite crônica com polipose nasal em tratamento com dupilumabe. São descritos os aspectos clínicos e o impacto na qualidade da vida do paciente. Imagens tomográficas evidenciam a melhora do processo inflamatório e a regressão dos pólipos nasais.

Descritores: Imunobiológico, rinossinusite crônica com polipose nasal, anticorpo monoclonal, interleucina-4, interleucina-13, dupilumabe.

Case report

A 64-year-old male patient sought care with an allergist due to a 10-year history of anosmia associated with controlled moderate asthma and hypersensitivity to nonsteroidal anti-inflammatory drugs. He reported multiple visits to the emergency room and using systemic corticosteroids to relieve respiratory symptoms, particularly anosmia and nasal discharge. He also reported previous intestinal infections due to an inability to smell spoiled food. Furthermore, the patient had undergone two polypectomies, the first one 20 years ago and the second one a year ago. He had a history of heart disease, hypertension, and diabetes. On physical examination, nasoscopy revealed widening of the nasal pyramid and bilateral polyps. The rest of the physical examination was normal. The patient had a total immunoglobulin E (IgE) level of 37.4, and skin tests and serum aeroallergen-specific IgE were normal. Figures 1 and 2 show the initial computed tomography (CT) scans of the paranasal sinuses.

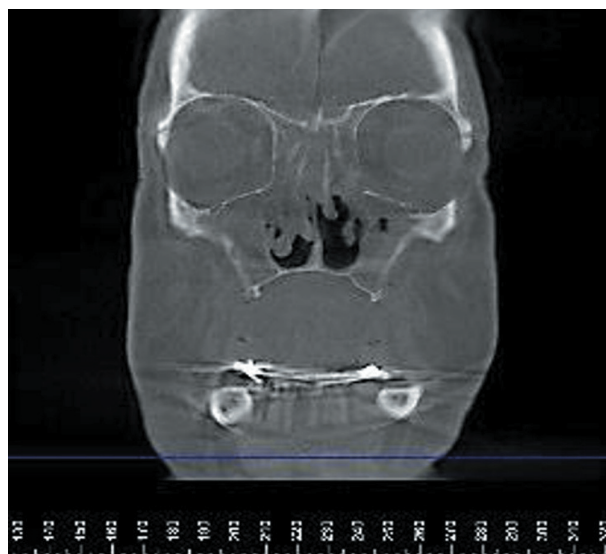


Figure 1

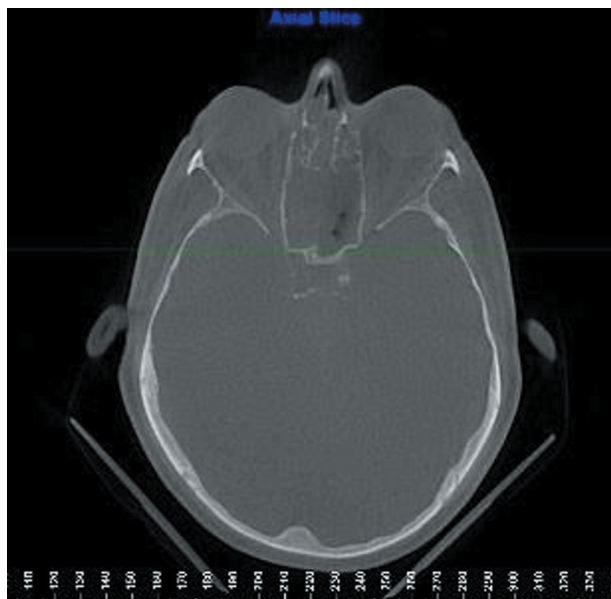
Axial plane showing complete opacification of the sphenoid sinus and the anterior and posterior ethmoid sinuses.

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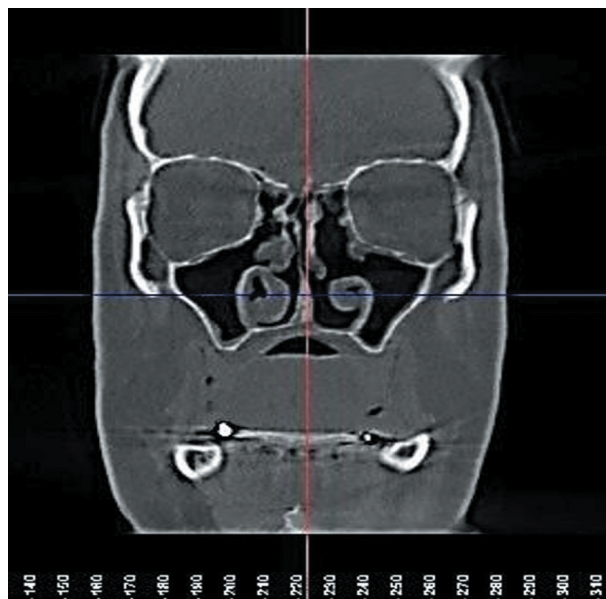
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**Figure 2**

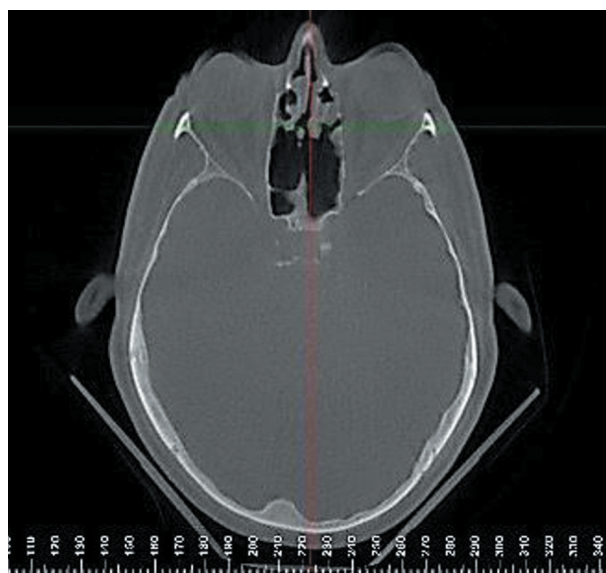
Coronal plane showing opacification of the ethmoid and maxillary sinuses and left inferior turbinate resection.

**Figure 3**

Axial plane showing regression of rhinosinusitis after 8 weeks of treatment.

After patient evaluation, the use of dupilumab was suggested due to the rapid recurrence of polyps, the adverse effects associated with systemic corticosteroids, and the surgical risk, considering the patient's multiple comorbidities. Treatment was initiated with an initial dose of dupixent 400 mg, followed by 200 mg every 14 days. The patient reported recovery of his sense of smell and improved breathing after the third injection. He no longer had intestinal infections due to inability to smell spoiled food, had control of his diabetes, and no longer used systemic corticosteroids. Figures 3 and 4 show CT scans of the paranasal sinuses after 3 months of dupilumab use.

In conclusion, we reported the case of a patient with chronic rhinosinusitis and severe nasal polyposis, with associated comorbidities and polyp recurrence within less than a year after surgery. Almost complete symptom control was achieved after the first injection of dupilumab, thereby improving the patient's quality of life and reducing the impact of systemic corticosteroid use on other comorbidities.

**Figure 4**

Coronal plane showing regression of rhinosinusitis after 8 weeks of treatment.

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Brazilian Guidelines to Allergen Immunotherapy for Patients with Allergic Rhinitis: Position Statement of the Brazilian Association of Allergy and Immunology (ASBAI)

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Dear Editor,

Allergen immunotherapy (AIT) is one of the cornerstones in the treatment of allergic diseases and the only therapeutic strategy with curative potential. It promotes the reduction of medication use and symptom control even after the end of treatment.¹

AIT is one of the procedures that define Allergy and Clinical Immunology as a specialty. Although it has been performed for over 100 years, doubts about its effectiveness and the actual benefits it provides to patients persist, particularly among non-specialists in the field.

Recently, the Brazilian Association of Allergy and Immunology (ASBAI) elaborated the “Good clinical practice recommendations in allergen immunotherapy: Position paper of the Brazilian Association of Allergy and Immunology”, which were published in a prestigious international journal in the field.¹ In this position statement, recommendations adapted to the Brazilian reality were established based on documents from the most prominent organizations in Allergy and Immunology in the world, always supported by evidence-based and precision medicine.¹ Nonetheless, the effectiveness and safety of subcutaneous (SCIT) and sublingual (SLIT) allergen immunotherapy, as well as their adverse events, indications, and relative and absolute contraindications in patients with allergic rhinitis still needed to be confirmed.

Therefore, ASBAI conducted a new systematic review evaluating the efficacy and safety of SLIT and SCIT in patients (adults and children) with allergic rhinitis (house dust mites and/or pollen). The initial database search yielded approximately 1,200 articles, of which only 47 met the inclusion criteria.² Twenty-five of them were double-blind, randomized, placebo-controlled trials, including a total of 4,518 patients with perennial allergic rhinitis, with or without associated asthma, and 3,887 placebo-treated control patients. The data obtained were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assign levels of evidence (high, moderate, low, and very low) and rate the strength of the recommendations (weak or strong).³ The effectiveness and safety of SCIT and SLIT in children and adults with allergic rhinitis (house dust mites and pollens) were evaluated (Table 1).

The criteria for indication and contraindication of SCIT and SLIT were also defined (Table 2).

Table 3 describes the criteria for monitoring the effectiveness and discontinuation of AIT.

The results of the systematic review showed that both SCIT and SLIT are effective and safe in the treatment of patients (children and adults) with allergic rhinitis (house dust mites and pollens) and that, whenever indicated, they should be part of the treatment regimen for these patients.

Table 1Subcutaneous (SCIT)* and sublingual (SLIT) allergen immunotherapy according to the GRADE recommendations³

	Level of evidence	Grade of recommendation
Is SCIT effective in children and adults with allergic rhinitis?	House dust mites – High Pollen – Moderate	Strong Strong
Is SCIT safe in children and adults with allergic rhinitis?	House dust mites – High Pollen – Moderate	Strong Strong
Is SLIT effective in children and adults with allergic rhinitis?	House dust mites – High Pollen – Moderate	Strong Strong
Is SLIT safe in children and adults with allergic rhinitis?	House dust mites – High Pollen – Moderate	Strong Strong

* It is recommended that SCIT be performed by the prescribing physician or under other medical supervision.

Table 2

Criteria for indication and contraindication of subcutaneous (SCIT) and sublingual (SLIT) allergen immunotherapy (AIT) in patients with allergic rhinitis

Criteria for indication
1 - Moderate-to-severe uncontrolled disease despite adequate environmental control and drug treatment; or if the patient does not wish to use medication. 2 - Confirmed diagnosis of immunoglobulin E (IgE)-mediated sensitization through skin prick test and/or serum-specific IgE. 3 - Correlation between allergic sensitization and symptom trigger. In practice, this correlation is clinical and, if possible, nasal and/or conjunctival provocation tests can be performed as well, although these procedures are typically reserved for studies. 4 - Patients aged 2 to 4 years for SLIT and over 5 years for SCIT, and patients aged up to 65 years with favorable clinical conditions for both therapies.
Relative (RCI) and absolute (ACI) contraindications
1 - Poorly controlled asthma and severe active disease (immunological, infectious, or neoplastic) – ACI. 2 - Eosinophilic esophagitis - ACI for SLIT . 3 - Controlled cardiovascular disease (use of ACE inhibitors, beta-blockers), controlled chronic disease, and mild psychiatric disease – RCI. 4 - Pregnancy and lactation – ACI for the initiation but not continuation of AIT. If in the induction phase, increasing concentration is contraindicated. 5 - Nonadherence – ACI for the initiation and continuation of AIT.

ACE = Angiotensin-converting enzyme.

Table 3

Criteria for monitoring the effectiveness and discontinuation of allergen immunotherapy (AIT) in patients with allergic rhinitis

Criteria for AIT monitoring
1 - Currently, the criteria for AIT monitoring are clinical, involving the evaluation of symptom and medication scores using consensus-based scales. This evaluation can be complemented by quality-of-life questionnaires. 2 - Assessment of adverse effects should be performed. 3 - There are no immunological markers available to monitor AIT. 4 - Skin prick testing should not be performed as a means of monitoring the efficacy or duration of AIT.
Recommendations for discontinuation of AIT
1 - Optimal AIT duration is 3–5 years after the beginning of the maintenance phase. AIT should be maintained for at least 3 years to achieve long-lasting efficacy. 2 - In case of pollinosis, AIT should be performed only for a few months before and during the pollen season. 3 - The skin prick test is not a good parameter for discontinuation of AIT, and there are currently no laboratory biomarkers to guide the duration of treatment. 4 - Clinical evaluation is always the best parameter to assess AIT efficacy. In case of lack of clinical results after reaching the maintenance dose, AIT should be discontinued.

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Acute management of perioperative anaphylaxis

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Dear Editor,

Although rare (with estimated incidence in the range of 1:353 to 1:18600 procedures), perioperative immediate hypersensitivity reactions are the most challenging clinical problems requiring drug allergy investigation. They are also a challenge for the surgical team, including the anesthesiologist who manages these cases directly. A combination of multiple anesthetic drugs, chemicals, surgical procedures, hidden exposures, and several differential diagnoses contribute to the challenge, making management of perioperative anaphylaxis complex. Collaboration between anesthesiologists, surgeons, and allergists is essential.¹ The European Academy of Allergy and Clinical Immunology (EAACI) position paper on this subject was important to guide correct investigation and management of these important events.²

Proper management of anaphylaxis during anesthesia requires prompt recognition and treatment, quantification of peak serum tryptase, and determination of the responsible agent. Signs and symptoms should be evaluated as well:

- Cardiovascular collapse or cardiac arrest, hypotension with or without tachycardia. Bradycardia may occur if the patient is highly hypovolemic or treated with beta-blockers.
- Bronchospasm is usually present in patients with underlying airway disease, such as asthma or COPD.
- Cutaneous presentation: urticaria, angioedema, and disseminated rash are frequent signs of anaphylaxis, but their absence does not exclude it.
- Gastrointestinal signs and symptoms may be present during regional anesthesia but are not common with general anesthesia, since fasting is required.

Differential diagnoses related to anesthetic and surgical procedures include systemic mastocytosis, mast cell activation syndromes and hereditary alpha-tryptasemia, uncontrolled surgical bleeding, bronchial hyperreactivity, adverse drug reactions, iatrogenic intubation trauma,

sepsis, thromboembolic event, cold-induced urticaria/anaphylaxis, and hereditary angioedema (HAE).

Systemic mastocytosis is a rare condition. The rate of immediate reactions related to anesthesia and surgery in patients with mastocytosis is only 0.4%. The physiological stress of surgical procedures and use of anesthetic and multiple analgesic agents, such as neuromuscular blockers and opioids, may be triggers of acute hypersensitivity reactions in this condition. Patients with mastocytosis require careful surgical management, especially when general anesthesia is contemplated. It is important to measure serum tryptase before surgery when mastocytosis is suspected (normal value: <11.4 ng/ mL). Elevated serum tryptase levels have been associated with an increased risk of systemic reactions. Several drugs, including neuromuscular blockers, can potentially activate mast cells through non-IgE MRGPRX2 receptors, thereby inducing mast cell-mediator release and consequently anaphylaxis.³

Acute Perioperative Anaphylaxis Management:

- Airway maintenance.
- 100% oxygen administration.
- Intravascular volume expansion.
- Epinephrine administration: preferably intramuscular epinephrine (0.5 mL of a 1 mg/mL solution) at the outer thigh (vastus lateralis muscle). An alternative route is to intravenously administer 1-3 mL of 1:10000 aqueous solution (0.1 mg/mL) over 10 minutes.⁴

Severe reactions may be difficult to treat and epinephrine may be given more than once (sometimes 3 injections), as well as larger doses of catecholamines, volume replacement and close intensive care observation.⁵ The American Society of Anesthesiology (ASA) has listed the following risk factors for fatal outcomes related to anaphylaxis: morbid obesity, increased patient age, coronary artery disease, beta-blockers and angiotensin converter antagonists, asthma, and malignancy.⁶ It is important to ensure that all possibly implicated factors and allergens are removed, such as chlorhexidine, latex, colloids, and drugs.

Post-anaphylactic reaction management:

- Evaluation of suspension of surgery depending on different factors: patient's physical condition, anaphylactic event severity, surgery status, and the urgency of the procedure. The risk/benefit ratio should always be considered.

- After anaphylaxis is controlled: administration of antihistamines and steroids, checking serum tryptase level, and patient transfer to an Intensive Care Unit.

There is no demonstrated evidence that supports pre-operative systematic screening in general patients. Allergy assessment must be performed in high-risk patients and in patients who have had an anaphylactic event during the perioperative context.⁷

When a cause is found, an adequate alternative should be recommended for drug groups with potential cross-reactivity.⁸ In approximately one-third of patients, no culprit could be identified.⁹ Suspected drugs should be investigated and when proven to be involved they should be avoided. Antibiotics, especially cefazolin, are among the major causes of IgE-mediated reactions and an elevated baseline serum tryptase level was associated with increased risk of recurrent perioperative allergic reactions.¹⁰

Despite intramuscular epinephrine being the first-line drug recommended to treat anaphylaxis, its use remains suboptimal. The dose recommended for use by healthcare professionals is 0.01 mg/kg of body weight, to a maximum total dose of 0.5 mg, given by the intramuscular route. Dosing should be repeated every 5-15 min if symptoms are refractory to treatment. Epinephrine administered by the intramuscular route is generally well tolerated. Regarding the intravenous route, arrhythmias can potentially occur because of bolus administration of epinephrine. For this reason, the intravenous route is not recommended for initial treatment of anaphylaxis and, if used, it should be administered to monitored patients by personnel experienced in diluting and administering the correct doses and should preferably be given as an intravenous infusion via an infusion pump. A number of protocols exist for low-dose epinephrine infusions via a peripherally-sited cannula to treat reactions refractory to intramuscular epinephrine. In Australia, New Zealand, and Spain these protocols are being developed as part of these countries' national anaphylaxis guidelines and have an excellent safety and efficacy profile. In case of upper airway obstruction, consider adding nebulized adrenaline.¹¹⁻¹³

Second-line medications include beta 2-adrenergic agonists, glucocorticoids, and antihistamines. Local guidelines may indicate different drugs according to availability.¹⁴ The use of H1- antihistamines has a limited role in treatment of anaphylaxis, but they can be helpful in relieving cutaneous symptoms. Second generation antihistamines may overcome unwanted side effects such as sedation, which may be counterproductive in anaphylaxis, but first generation H1-antihistamines are

currently the only class available for parenteral use (e.g., chlorpheniramine, diphenhydramine, promethazine, clemastine). Rapid intravenous administration of first-line antihistamines such as chlorpheniramine could potentially cause hypotension. Antihistamines are now a third-line treatment in some guidelines, due to concern that their administration can delay more urgent measures such as repeated administration of intramuscular epinephrine. Glucocorticosteroids are commonly used in anaphylaxis, with the goal of preventing protracted symptoms, especially in patients with asthmatic symptoms, and also to prevent biphasic reactions (intravenous hydrocortisone or methylprednisolone). However, there is increasing evidence that glucocorticosteroids may be of no benefit in the acute management of anaphylaxis, and may even be harmful, so their routine use is currently controversial.^{15,16} Parenteral administration of glucagon may be used in patients with anaphylaxis with no optimal response to epinephrine, in patients taking beta-blockers, despite very limited evidence. Glucagon may have a role in anaphylactic cases associated with severe inotropic cardiac dysfunction.¹⁷

Around half of biphasic reactions occur within the first 6-12 h following an anaphylactic reaction. Patients with anaphylaxis need to be observed: this is important especially in severe reactions, and in those requiring multiple doses of epinephrine.^{18,19}

A follow-up investigation should be conducted after a perioperative immediate hypersensitivity event to establish a diagnosis and to provide advice for subsequent anesthetics. The main risk factor for perioperative IgE-mediated anaphylaxis is a previous uninvestigated perioperative immediate hypersensitivity reaction.

The concept of cross-reactivity between drugs used in the perioperative setting and foods is often quoted, but is usually not supported by evidence. There is no reason to avoid propofol in egg, soy, or peanut allergy. The allergenic determinants have been characterized for fish, shellfish, and povidone iodine, but remain unknown for iodinated contrast agents. Iodinated contrast agents may be used in seafood allergy. Evidence supporting the risk for protamine allergy in fish allergy and in neutral protamine Hagedorn insulin use is lacking. Cross-reactivity to gelatin-based colloids may occur in α -gal syndrome.

Atopy and allergic asthma and non-allergic conditions, such as NSAID-exacerbated respiratory disease, chronic urticaria, mastocytosis, and hereditary or acquired angioedema are not risk factors for IgE-mediated drug allergy, but there is a perioperative risk associated with the potential for clinical exacerbation of these associated conditions.²⁰

Most patients safely undergo subsequent anesthesia after a proper Allergy and Immunology evaluation. Cooperation between anesthesiologists and allergists/immunologists is of extreme importance for a successful approach in the diagnosis, investigation, and management of perioperative anaphylaxis.²¹

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Collaboration between Allergy and Anesthesia

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Dear Editor,

Perioperative immediate hypersensitivity reactions are rare (range of 1:353 to 1:18600 procedures). They are a challenge for the surgical team and especially for the anesthesiologist, who bears most of the responsibility for outcomes. Many drugs, chemicals, and associated procedures play a role in their pathogenesis. Collaboration between specialists in the field of anesthesiology and allergy-immunology is essential for successful evaluation and care of these patients. Allergic and non-allergic mechanisms may be present.¹ Situational awareness is always crucial.² Therefore, managing the patient experiencing perioperative anaphylaxis requires close collaboration between anesthesiologists, surgeons and allergists.³ The European Academy of Allergy and Clinical Immunology (EAACI) are currently promoting this important interaction.⁴

The fact is that the majority of patients safely receive subsequent anesthesia after proper allergic evaluation for their perioperative hypersensitivity reactions, although an elevated baseline serum tryptase level poses an increased risk of recurrent perioperative allergic events. The main culprits are neuromuscular blocking agents, latex, cefazolin and other antibiotics, and dyes.⁵

Any drug or blood product administered in the perioperative period has the potential to produce anaphylaxis. Rapid and timely cardiovascular and pulmonary intervention is required and includes patent airway maintenance, epinephrine administration, and volume expansion correcting the potentially dangerous associated hypotension.⁶ An alternative to intramuscular epinephrine (0.3-0.5 cc of 1mg/mL solution) is to intravenously administer 1-3 cc of 1:10000 aqueous solution (0.1mg/mL) over 10 minutes.⁷ *In vitro* diagnosis of immediate drug hypersensitivity during anesthesia has mainly been investigated for neuromuscular blocking agents, beta-lactams, latex, and chlorhexidine.⁸

The important causes of perioperative anaphylaxis are as follows: neuromuscular blocking agents, antibiotics, latex, chlorhexidine, blue dyes, opioids, non-steroidal anti-inflammatory drugs, anesthetic agents, plasma expanders,

oxytocin, ethylene oxide, excipients, sugammadex, and blood products. Since the protease “tryptase” is released from the cytoplasm of degranulating mast cells during anaphylaxis, systemic mastocytosis, mast cell activation syndromes, and hereditary alpha-tryptasemia should also be ruled out. An increase of serum tryptase is documented by the formula: baseline tryptase x 1.2 + 2ng/mL. Baseline tryptase can be obtained about 24 hours after the anaphylactic episode. *In vitro* testing can also include: plasma histamine, urinary methylhistamine, PGD₂, PGF₂-alpha, and LTE₄, and also specific IgE testing (sIgE), basophil activation test (BAT), and histamine release quantified by flow cytometry (HR). However, the gold standard is drug provocation testing (DPT). *In vivo* skin testing (prick and intradermal tests) is universally used in cases of perioperative anaphylaxis.¹

When a cause is found, an appropriate alternative should be recommended for drug groups with potential cross-reactivity.⁹ Suspected drugs should be investigated and, when proven to be the culprits, they should be avoided and extra monitoring should also be employed for effective management of any potential future anaphylaxis.

Anesthesiologists frequently ask allergists questions like the ones listed below and these should be carefully addressed:

- How can the cause of perioperative anaphylaxis be identified?
- When should surgery be interrupted?
- Which is best, intramuscular or intravenous epinephrine injection?
- How long after an epinephrine injection should another one be considered?
- After the anaphylactic episode, should a post-op intensive care unit be recommended?
- What about future anesthesia?

A close and strong bond should always exist between the surgical and the allergy teams when dealing with perioperative immediate hypersensitivity reactions. One critical factor for successful management of perioperative hypersensitivity is therefore direct and intense collaboration between the anesthetist involved and the allergy teams.¹⁰

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Proposed Constitutional Amendment (PEC) No. 10 of 2022: Manifestation of the Scientific Department of Inborn Errors of Immunity of the Brazilian Association of Allergy and Immunology (ASBAI)

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The Brazilian Association of Allergy and Immunology (ASBAI) is composed of medical specialists in Allergy and Clinical Immunology responsible for the diagnosis and care of patients with primary immunodeficiency disorders (PIDs), more recently referred to as inborn errors of immunity. The most common PIDs, according to global experience, are those affecting antibody production. In these cases, the main clinical manifestations are infections, which can range from mild and recurrent to severe, requiring hospitalization for intravenous treatment. These infections can result in pulmonary, auditory, and other sequelae and may even lead to death in many situations.

The primary treatment for these patients is immunoglobulin (Ig), obtained through the collection of human plasma from many donors. For decades, patients, as well as the medical specialists who care for them, have suffered from periodic Ig shortages in Brazil and the dire consequences associated with it. Despite numerous proposals, we remain dependent on the importation of these products, as Brazil does not produce a single drop of Ig.

In recent years, particularly during the pandemic, when Ig became increasingly difficult to acquire, the Brazilian Ministry of Health began procuring products that were not approved by the Brazilian Health Regulatory Agency (ANVISA), arguing that Fiocruz's National Institute of Quality Control could perform the same type of safety and efficacy analysis as ANVISA. Despite the pandemic being under control and the resumption of plasma collection and Ig production in other countries, the Brazilian Ministry of Health maintained this stance. ASBAI, as well as patient associations, expressed opposition to this decision, as this flow could clearly compromise the quality and safety of treatment for patients using Ig. Unfortunately, the arguments presented by the parties responsible for product use and the patients themselves were NOT considered.

Indeed, it is of paramount importance that Hemobrás produces Ig in Brazil and that we stop being completely dependent on imported products. This is expected to happen by the end of 2025, according to information provided by the Federal Government. However, we estimate that production, while welcome, will most likely not meet the demand for Ig, which has been growing worldwide.

Plasmapheresis represents a significant advancement in the collection of plasma, from which many products necessary for the well-being of thousands, perhaps millions, of Brazilian citizens are obtained. It is important to note that although our focus has been on antibody deficiency, patients with neurological, rheumatologic, hematological, and other diseases also require and use human Ig. Additionally, various derivatives such as albumin, coagulation factors, and complement proteins, which are essential for the treatment of various diseases, are obtained from human plasma.

The European community, concerned with ensuring the supply of Ig for a growing number of patients, is revising its legislation. A populous country with continental dimensions like Brazil should do the same. We also share concerns regarding the commercialization of plasma, which is precisely why we believe that the legislation should be reviewed, improved, and meticulously drafted to respect the principles of the 1988 Constitution of Brazil while ensuring that our patients are respected and receive adequate care. We would like to note that our health care model, the Brazilian Unified Health System, is a source of pride and, at this moment, we must demonstrate our ability to provide adequate treatment for our Brazilian patients and citizens.

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