ISSN 2764-6335

Arquivos de Asma, Alergia e Imunologia

ASBAI – Associação Brasileira de Alergia e Imunologia

SLaai – Sociedad Latinoamericana de Alergia, Asma e Inmunología

Volume 7 • Number 2 • April-June 2023

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Arquivos de Asma, Alergia e Imunologia is the official organ of the Associação Brasileira de Alergia e Imunologia for scientific publications. All correspondence should be sent to the ASBAI's Publishing Department - Rua Domingos de Morais, 2187 - 3º andar - salas 315-317 - Bloco Xangai - Vila Mariana - CEP 04035 -000 - São Paulo - SP - Phone: (11) 5575.6888 – E-mail: aaai@asbai.org.br – Home page: www.asbai.org.br

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"Arquivos de Asma, Alergia e Imunologia" is the quarterly scientific publication of the **Associação Brasileira de Alergia e Imunologia**, Rua Domingos de Morais, 2187 - 3º andar - salas 315-317 - Bloco Xangai - Vila Mariana - CEP 04035 -000 - São Paulo - SP - Brazil - Tel.: 55 (11) 5575.6888 - E-mail: aaai@asbai.org.br - Home page: www.asbai.org.br.

| English translation: Scientific Linguagem. | Production, editing and commercialization: Arte e Composição Ltda. - Tel.: 55 (51) 3026.5031 / (51) 991772047. E-mail: artecomp@terra.com.br.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Action of immunobiologics in asthma remission

Ação dos imunobiológicos na remissão da asma

Pedro Giavina-Bianchi[1]

Asthma is a syndrome of high prevalence and morbidity, which has a substantial social and economic impact and can even be fatal. In this context, several organizations and medical societies have developed consensus statements and guidelines for the optimal approach to asthma, among which we highlight the Global Initiative for Asthma (GINA) developed by the World Health Organization. GINA promotes several actions with the aim of improving asthma management while minimizing morbidity resulting from the disease and the risk of premature death, which would enable patients to lead a productive and fulfilling life.[1]

There has been a clear improvement in the approach to and management of asthma in recent decades. Statistics on hospital admissions for asthma in the Brazilian Unified Health System, responsible for the care of approximately 70% to 75% of the Brazilian population, show a drop in the admission rates since 2000, when there was a peak of 397,000 hospitalizations. Currently, there are less than 100,000 hospitalizations for asthma per year, corresponding to a 75% reduction. Factors that may have contributed to this decrease in morbidity include the development and implementation of consensus statements and care programs for patients with asthma in Brazil, including the availability of medications, especially inhaled corticosteroids. However, already-initiated actions need to be improved and made less heterogeneous in the different regions of the country, given that approximately 2000 patients still die of asthma[2] per year.

In this issue of the Arquivos de Asma, Alergia e Imunologia, Mello L.M. and Cruz A.A. analyze the structure of the Brazilian health care system and discuss key aspects of integrated care for asthma.[3] Also in this issue, Urrutia-Pereira M. and Solé D. present a summary of the Lancet Countdown South America report, the result of a multidisciplinary academic collaboration between academic institutions and South American health agencies from 12 countries, which was published by Hartinger et al. (2023). This study is a wake-up call, as it publishes the results of the survey on climate change and its effects on human health in South America, highlighting the effects on the respiratory system. Being aware of these results is the first step to implementing public health policies, preferably in a preventive setting.[4]

In parallel with the improvement in asthma treatment and the development of new drugs, the goals of this treatment have also been improved.

Editor of the Arquivos de Asma, Alergia e Imunologia (AAAI).
Associate Professor – Division of Clinical Immunology and Allergy, FMUSP - São Paulo, SP, Brazil.
Visiting Professor at Harvard Medical School 2012-2014.
Director of the World Allergy Organization.

Arq Asma Alerg Imunol. 2023;7(2):133-5.

http://dx.doi.org/10.5935/2526-5393.20230018-en

The first goal used to be disease control and then prevention of future risks associated with asthma: exacerbations, lung function loss, and adverse reactions to treatment.[1,5] Over the past decade, the goal of the treatment of chronic diseases that have periods of exacerbation has shifted to induction of sustained remission whenever possible or, when this goal is unachievable, attainment and maintenance of the lowest disease activity. This concept was first established in the treatment of rheumatoid arthritis, with a change in treatment from corticosteroids to disease-modifying antirheumatic drugs, including more recently biologics for the treatment of more severe cases.[6]

In 2020, the first results were published from a project aiming to reach a consensus definition of asthma remission and to make it the main treatment goal.[7] The idea is for the project to be continuous and interactive. Regarding remission, patients can be divided into 4 groups: clinical remission on and off treatment and complete remission on and off treatment (Table 1). In clinical remission, patients must be asymptomatic and without exacerbation for 12 months. Patients may be using medication, including high doses, but with no use of systemic corticosteroids. Lung function should preferably be normal, but this may not be achievable for patients with long-term disease, receiving inappropriate treatment, or experiencing airway remodeling. Some authors argue that patients with lung function stabilization, with values close to normal, may be considered in remission.[7] Other authors consider an improvement of 100 mL in FEV_1 in relation to pre-treatment optimization values a remission criterion.

Reanalysis of several clinical trials that proved the efficacy and safety of monoclonal antibodies in the treatment of severe uncontrolled asthma has shown that these biologics help patients achieve clinical asthma remission. An analysis of the German registry of patients with severe asthma showed that the group of patients receiving a monoclonal antibody had better rates of good response to treatment (61.4%) and clinical remission (37.6%) than the group not receiving a biologic (34.8% and 17.2%, respectively).[8]

We have all come across a recurring question from patients: can asthma be cured? We need to be careful with the answer and explain that, although we cannot talk about a cure, the goal of treatment is to achieve disease remission. Once this has been made clear, the patient will be more likely to participate and adhere to treatment, increasing the chances of success. It is important to highlight that asthma remission does not mean asthma cure, and that being in remission does not completely eliminate the risk of a severe and even fatal exacerbation of the disease. From our first classes on asthma, we learn that the treatment of the disease begins with patient counseling and education, and that the patient must understand the difference between maintenance therapy and treatment of attacks, being able to manage both situations, including a written action plan.

Table 1
Asthma remission (the patient must remain in this condition for 12 months and there must be patient/physician agreement regarding disease remission)

	On treatment / Off treatment
Clinical	Clinical status (asymptomatic, no exacerbations; ACT, ACQ), pulmonary function test (stable, normal, or close to normal), no systemic corticosteroids
Complete	Normalization of blood eosinophil counts, FeNO, nonspecific bronchial provocation test

ACT = asthma control test, ACQ = asthma control questionnaire, FeNO = fractional exhaled nitric oxide.

Asthma remission is an ambitious goal, but it is crucial to fully restore health in our patients, enhancing patient empowerment and quality of life.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Climate change and its impact on human health in South America

Alterações climáticas e sua repercussão sobre a saúde humana em países da América do Sul

Marilyn Urrutia-Pereira[1,2,3,4], Dirceu Solé[2,5,6,7]

ABSTRACT

Climate change has intensified in the last two decades, damaging the environment and those who inhabit it. Human activity has increased the prevalence and intensity of these changes. Increased social inequality and vulnerability, deforestation, intentional forest fires, soil degradation, and environmental pollution, when associated with sea temperature variability, can lead to extreme weather events, increasing negative health effects. This report summarizes *Lancet Countdown South America* (Hartinger et al. 2023), the result of multidisciplinary collaboration between education institutions and South American health agencies from 12 countries: Argentina, Bolivia, Brazil, Colombia, Chile, Ecuador, Guyana, Paraguay, Peru, Uruguay, Venezuela and Suriname. This should be considered a wake-up call because it contains the results of a climate change survey and its effects on human health in South America. Knowing these effects is the first step toward appropriate, preferably preventive, public health policies.

Keywords: Climate change, human health, deforestation, forest fires.

RESUMO

Nas últimas duas décadas as mudanças climáticas têm se intensificado, causado danos ao meio ambiente e aos indivíduos que nele habitam. Várias ações do ser humano têm contribuído para que cada vez mais essas mudanças climáticas sejam mais presentes e intensas. O aumento das desigualdades e vulnerabilidades sociais, o desmatamento, os incêndios florestais voluntários, a degradação do solo e a poluição ambiental aliados à variabilidade climática global da temperatura da água do mar podem potencialmente levar a eventos climáticos extremos, potencializando os efeitos negativos sobre a saúde. Neste trabalho é apresentado um resumo do relatório do *Lancet Countdown South America*, fruto da colaboração acadêmica multidisciplinar de instituições de ensino e agências sul-americanas de saúde de 12 países (Argentina, Bolívia, Brasil, Colômbia, Chile, Equador, Guiana, Paraguai, Peru, Uruguai, Venezuela e Suriname) publicado por Hartinger e cols. (2023). Este estudo é uma alerta, pois nele são publicados os resultados do levantamento sobre mudanças climáticas e seus efeitos sobre a saúde humana no continente sul-americano. Conhecê-las é o primeiro passo para que políticas de saúde pública sejam instituídas, e, preferencialmente, de modo preventivo.

Descritores: Mudanças climáticas, saúde humana, desmatamento, incêndios florestais.

1. Medical School, Universidade Federal do Pampa - Uruguaiana, RS, Brazil.
2. Department of Pollution, Latin American Society of Allergy, Asthma and Immunology - SLaai.
3. Coordinator of the Biodiversity Commission, Brazilian Association of Allergy and Immunology (ASBAI).
4. Scientific Department of Toxicology and Environmental Health, Brazilian Society of Pediatrics (SBP).
5. Department of Pediatrics, Universidade Federal de São Paulo – Escola Paulista de Medicina – EPM/UNIFESP) – São Paulo, SP, Brazil.
6. ASBAI Research Director.
7. SBP Scientific Director.

Submitted Apr 05 2023, accepted Apr 14 2023.
Arq Asma Alerg Imunol. 2023;7(2):136-42.

http://dx.doi.org/10.5935/2526-5393.20230019-en

Introduction

Climate change has become increasingly present and intense.[1-5] Weather-related events are responsible for damage to the environment as well as to the individuals who inhabit it. Increased social inequalities and vulnerabilities, deforestation, land degradation and global climate variabilities in sea temperature can potentially lead to extreme weather events, enhancing the negative effects on health.[1-5] Understanding the real dimension of the problem, even at the regional level, is the first step to implementing effective adaptation and mitigation measures to avoid and prevent its deleterious effects on human health.

In a recent study, Hartinger et al. published the results of a survey on climate change and its effects on human health in the South America, called Lancet Countdown South America (LCSA).[6] The LCSA was generated by a multidisciplinary academic collaboration that brought together 21 academic institutions and South American agencies of the United Nations from 12 countries (Argentina, Bolivia, Brazil, Colombia, Chile, Ecuador, Guyana, Paraguay, Peru, Uruguay, Venezuela, and Suriname; French Guiana was not considered), led by 28 researchers representing various disciplines. The LCSA aimed to assess the relationship between public health and climate change in South America.

The data and results provided in this report represent the consensus of various experts across multiple fields who have participated in the LCSA and are part of the 2022 global report of the Lancet Countdown.[2] The report brings together several indicators that provide the evidence to support targeted response strategies for decision-makers.

Given the relevance of the topic and the moment we live in, we present below a summary of the 4 main conclusions of the report, in the form of messages.[6]

Climate change is harming the health of South Americans, it's time to take prompt action

The adverse health effects of climate change are accelerating and have disproportionately affected the most vulnerable populations in South America. For the past 10 years, these populations have had their health increasingly affected by climate change-related hazards, and unless actions are taken, this trend will get worse.

In the last 10 years, more frequent and intense heat waves have put children under 1 year of age and adults over 65 at risk. Children aged < 1 year were exposed to an estimated 2.35 million more person-days of heat waves each year, and adults aged ≥ 65 years to 12.3 million more person-days, as compared to a 1996-2005 baseline.

Since the year 2000, an increase in the estimated number of heat-related deaths has been observed among people aged ≥ 65 years in all countries, being more pronounced in Brazil, Argentina, Colombia, and Venezuela. The cost of these deaths was estimated to correspond to the average income of 485,000 local workers in 2021. Furthermore, the potential regional income loss associated with heat-related reduction in labor productivity in 2021 was US$22 billion, with the construction and agriculture sectors being the most severely affected, with 68% of the total losses occurring in the region.

Elevated temperatures and increased incidence of droughts, especially in the past decade, have led to an increase in the occurrence of wildfires and exposure of the populations living in these regions. In addition, another aggravating factor that occurs in South America is human-made wildfires, which are more closely related to land use change and deforestation, as seen in the Amazon. Regionally, population exposure to very high or extremely high wildfire danger in South America increased in 9 of 12 countries, with an average increase of 7 more days in 2018-2021 compared to the reference baseline.

Climate change, by changing environmental conditions (more intense and prolonged droughts, extreme weather events, higher temperatures, and increased atmospheric CO_2 concentrations), also interferes with food systems, affecting the growth, yield, and nutritional content of several crops, including 4 staple crops (wheat, rice, maize, and soybean). This is of particular concern given that 168.7 million South Americans are affected by moderate or severe food insecurity. The average duration of the growing season for spring wheat, winter wheat, maize, soybean, and rice decreased by 2.5%, 2.2%, 1.6%, 1.3%, and 0.4%, respectively, compared to the reference baseline (1981-2010). Therefore, these impacts threaten the livelihoods of people who depend on the agricultural sector and pose a serious threat to food security in the region.

The changing environmental conditions have also affected the geographic distribution of infectious

diseases. The region is endemic for dengue, which is responsible for a high disease burden and frequent epidemic cycles across the region. Dengue transmission has reached its highest level in recent years, with an increase of 35.3% in 2012-2021 compared to the 1951-1960 reference baseline, especially in countries where *Aedes aegypti* is found. Other factors, such as urbanization and mobility, also interfere with the spread of dengue. In Brazil and Peru, there has been an increase in its spread to higher latitudes and less populated areas.

Climate change can also trigger viral sharing among previously geographically isolated wildlife species, leading to cross-species transmission and disease emergence. In addition to the increased risk of dengue posed by climate change, temperate Southern Cone countries are highly vulnerable to the severe effects of dengue, mainly driven by rapid urbanization. Argentina and Uruguay experienced increased vulnerability between 1990 and 2019.

South American countries must increase their preparedness to protect populations from the health impacts of the climate crisis

Understanding, assessing, and monitoring the health impacts of climate change and health co-benefits of climate actions is essential for the development of adaptation plans and policies that can protect the health of South American populations against increased flooding, as a result of climate change, and maximize their positive impact.

In view of rapidly increasing health risks resulting from climate change, countries should focus efforts on identifying their specific risks, as well as on developing appropriate adaptation plans. At the subnational level, few municipalities have conducted city-level climate change risk assessments, which raises concerns about whether the data, needs and differences between countries at the local level are being integrated into the National Adaptation Plans (NAPs).

Reflecting the insufficient planning for health adaptation, South American countries have not provided adaptation responses proportionate to the growing risks faced by their populations. Adaptation actions, such as expanding urban green spaces, strengthening health systems, and building more resilient essential infrastructure, have the potential to reduce climate-related health impacts and promote health and well-being. However, of the 73 urban centers surveyed in 2021, 84% had very low or exceptionally low levels of green space, and only 12 (16%) had moderate levels. These results reflect the limited progress in the implementation of an effective adaptation measure that may not only reduce exposure to health-threatening extremes of heat in urban areas but also provide significant direct benefits through cleaner air, improved mental health and well-being from exposure to green space, and improved overall health outcomes from access to spaces for socialization and recreation.

Improving the health system capacity and resilience is essential because, with the increase in health risks associated with climate change, the population's health needs also increase. Therefore, efforts made by government agencies should focus on ensuring that health facilities have access to the essential services they need to provide adequate care, including water and sanitation services, electricity supply, and Internet connectivity. Health-care infrastructure must also be strengthened to deal with the increasing effects of extreme weather events and to be safe strongholds during climate-related emergencies. The health system capacity must be adjusted to meet the growing demand for care, and resources must be allocated to training and educating health professionals so that they can recognize, prevent, and treat the health consequences of climate-related hazards.

Surveillance, early warning and early response systems must be implemented in collaboration with meteorological agencies and tailored to the local health risks in order to inform the prevention and appropriate response to these health risks. In fact, the call for universal coverage of early warning systems against extreme weather events and climate change was enshrined in the agreement reached in the 2022 United Nations Climate Change Conference or Conference of the Parties to the United Nations Framework Convention on Climate Change (UNFCCC; COP27). However, only Argentina and Brazil report incorporating climate information for heat early warning systems in their health systems. The heat early warning system in Argentina is the only national early warning system that has been implemented and evaluated.

Strengthening South American health systems to better prevent and respond to climate-related health risks will also provide better services, with overall

gains to the health and well-being of the populations. With the fragility of health systems exposed during the COVID-19 pandemic, strengthening local health services should be a priority in local government agendas.

South America must continue and accelerate efforts toward the race to zero-carbon transition

Efforts must be continued and accelerated to mitigate greenhouse gas (GHG) emissions, reduce changes in land use linked to deforestation, decarbonize the energy and transport system, and increase the production and use of renewable energy. Doing so will not only help the region meet its commitments under the Paris Agreement but also provide significant health benefits through improved air quality, reduced energy poverty, reduced inequalities in access to transport, and more active lifestyles.

Although South America is responsible for only 6% of global GHG emissions, it must join efforts to reduce them and, more importantly, to ensure that it is not left behind in the global transformation toward a much healthier, net zero emission system. These emissions are mainly related to land use change (24%), agriculture (28%), and energy production (39%). Therefore, mitigation related to land use and agricultural practices is especially important, requiring a long-term strategy, national and international incentive systems, and strong governance and regulations, which are particularly challenging in South American countries.

Climate change mitigation in the agricultural sector and in land use change linked to deforestation also has the potential to provide significant simultaneous and immediate health benefits to local populations and promote healthier diets, with the additional benefit of reducing premature death from imbalanced diets. In South America, 23% of all deaths attributable to imbalanced diets are related to high intake of red and processed meat and dairy products, whose production is highly carbon intensive (mainly due to emissions associated with livestock feed production and enteric fermentation of ruminants). Therefore, minimizing red meat intake as per dietary guidelines would not only help prevent these deaths but also reduce GHG emissions related to livestock and associated agricultural practices.

Regarding the energy sector, mitigation may also provide substantial and immediate health co-benefits. The burning of fossil fuels not only contributes to increasing GHG concentrations in the atmosphere but also leads to toxic levels of pollution in the air that people breathe. In South America, exposure to particulate matter 2.5 (PM2.5) in outdoor air caused 37,000 deaths in 2020 alone, with the highest death rates being observed in Chile (230 deaths/million) and Peru (178 deaths/million). The costs resulting from premature mortality due to air pollution correspond to the average income of 2.9 million productive people.

Switching to clean fuels can also significantly reduce exposure to household air pollution and reduce urban-rural health inequalities. Despite the near-universal access to electricity in South American homes, only half is generated from clean sources such as solar, wind, or hydropower. Furthermore, there are large urban-rural differences, with 23% of the rural population still relying exclusively on biomass fuels for cooking, exposing them to high levels of indoor air pollutants. The annual average exposure to PM2.5 of a rural household is 171 $\mu g/m^3$ (95% CI, 159-183), 34 times higher than the annual threshold of 5 $\mu g/m^3$ recommended by the World Health Organization.

Decarbonizing road transport may also provide important benefits to the health of South American populations. Reducing fossil fuel-based road transport may help prevent deaths attributable to exposure to PM2.5 air pollution generated by the transport sector, with more than 10,100 deaths being recorded in 2020. Expanding access to and use of safe, affordable, and reliable public transport networks would not only reduce the use of fossil fuels but also provide important co-benefits from reducing socioeconomic inequalities associated with transport access. Moreover, promoting modal shift toward active forms of transport through incentives and safe infrastructure can simultaneously provide significant physical and mental health benefits associated with increased physical activity.

Despite these potential health benefits, South American countries increased their per capita energy use for road transport by 138% between 1971 and 2019. Specifically, countries such as Paraguay, Ecuador, Bolivia, and Guyana have tripled their per capita energy use in road transport since the 1970s. This occurred in parallel with the

rapid urbanization process and regional increase in motor vehicle sales.

Fossil fuels remain the main energy source for road transport in South America (84%), followed by biofuels (16%). Although often regarded as a sustainable alternative, biofuels cause net carbon emissions (especially first-generation biofuels), their production typically generates net emissions from land use change, and, most importantly, their combustion emits air pollutants, such as PM2.5, that harm human health. Even in Chile and Ecuador, countries that lead the electrification of road transport in the region, less than 1% of the road energy sources comes from electricity. In the region, electricity accounts for only up to 4% of the energy used in road transport.

As the global energy crisis drives sharp increases in international energy prices and the rising inflation threatens people's ability to afford clean energy, energy poverty in the region is likely to increase, and with it so is the use of harmful fuels in people's homes. Rapid action to phase out the use of fossil fuels in the region and increase the local production of clean, renewable energy at all levels (i.e., individual, household, community, and society) would not only help meet the commitments that countries have made in the Paris Agreement but also provide more resilient, stable, and sovereign energy systems for South American populations. This, in turn, would reduce the region's dependence on volatile international fossil fuel markets and geopolitical conflicts, help reduce energy poverty and its associated health impacts, and improve the quality of the air that people breathe across the region.

Concerningly, despite the dangers that the continued overdependence on fossil fuels represent for South American populations, countries in the region continue to offer financial incentives for fossil fuel consumption, hindering the transition to clean, renewable energy sources. Considering all subsidies and carbon pricing instruments, the region continues to effectively subsidize fossil fuel consumption, for a total amount equivalent to an average of 10.5% of government spending on health in the region. Currently, net fossil fuel subsidies in Venezuela, Ecuador, Bolivia, and Argentina account for 85.6%, 29.2%, 23.5%, and 15.4%, respectively, of the national health budget. These net subsidy equivalents range from 3.5% to 4.8% for Brazil, Chile, and Colombia. In total, the 6 countries spent US$27.9 billion on fossil fuel subsidies in 2021. Redirecting this spending toward subsidizing renewable energy and protecting vulnerable populations from the rising energy costs and living costs of the energy crisis would not only promote the transition to a healthy, low-carbon future but also contribute to reducing inequalities and energy poverty.

South American countries require serious financial commitments to respond to the challenges imposed by climate change

Implementing climate change adaptation policies and actions for the health and well-being of populations is a no-regrets investment that requires government support, with transparent financial commitments and concrete budget allocation.

Although South American governments have submitted their second round or updated versions of their Nationally Determined Contributions (NDCs), only 8 of the 12 countries submitted revised NDCs by 2021. The percentage change in the number of mentions of health-related terms from the first to the second NDC was 130.4%. The countries with the largest number of mentions were Venezuela, Paraguay, and Colombia. This reflects the awareness of the links between health and climate change and the prioritization of the national climate agendas. However, many of these NDCs are high-level commitments that consolidate a country's intention, in some cases without fully detailing the activities, indicators to monitor its progress, institutional roles and responsibilities, and/or a budget for its implementation. Typically, this more detailed description is developed in NAPs and in sectoral NAPs – in the case of health – a Health NAP. Despite the high-level recognition of the importance of having health-related activities in the countries' NDCs, only Brazil developed a Health NAP by 2021, while other countries (Argentina, Colombia, Chile, and Peru) report having them ready but not submitted or under development.

Despite the urgent need to protect the health of local populations given the rapidly increasing health hazards, health care adaptation is woefully underfunded in South America, with only 10% (US$36 million) of approved adaptation-related funding dedicated to health in 2021. However, the large sums of money allocated to subsidizing fossil

fuels show that funds are often available but not allocated to activities that would enable a safe and healthy future.

Social and infrastructure spending required to meet climate goals ranges from 7% to 19% of gross domestic product by 2030 (US$470,000 to US$1,300,000 million in 2030) depending on initial conditions and proposed economic and social targets. From this perspective, a just transition to a sustainable future requires sufficient funds to be made available to less industrialized countries, including many South American countries. Less industrialized countries need to be empowered to transition to healthy, resilient, zero-carbon energy systems and stronger, better prepared health systems. At COP27, "developed" countries were urged to increase their contribution of climate finance, technology transfer and capacity building to respond to the adaptation and mitigation needs of "developing" countries. Implementing this ambition, which should be advanced at COP28, is essential not only to achieve the goals of the Paris Agreement but also to achieve better and more equitable global health.

The implementation of accelerated climate measures requires support from key actors and sectors of society, such as policymakers, scientists, the media, and the general public. Effective science communication on the links between climate change and health is critical to changing public perceptions, generating demand for action, and informing the implementation of evidence-based adaptation and mitigation policies that maximize health benefits. Media coverage of the relationship between health and climate has increased in South America, reaching an all-time high in major newspapers from 8 countries in 2021. And while the health dimension of climate change remains understudied in the region, original research led by South American researchers has increased by more than 1000% since 2007. Nevertheless, 94% of published articles on health and climate change refer to climate effects on health, while the number of those on the effects of multisectoral action (health co-benefits and adaptation) on climate and health remains low. Research on the benefits of health-focused climate action is urgently needed in South America to inform an evidence-based mitigation and adaptation response that maximizes the benefits to local populations.

The inaugural LCSA report focuses on (a) the immediate health threats posed by climate change in South America, (b) the limited health adaptation plans developed in the region, (c) our need to accelerate efforts toward the race to zero-carbon transition, and (d) the existing financial gap to address the health burden of climate change in South America. Furthermore, the report highlights the need to promote regional efforts in order to build resilient health systems and reduce the converging effect of inequality, poverty, and vulnerability in the face of climate change. Never has it been more important to work toward the Paris Agreement to limit the global average temperature increase to 1.5 °C and to free up the financial resources needed for an effective climate response. In addition, such climate action may provide immediate and substantial benefits, saving millions of lives each year, by improving air quality as well as diet and physical activity, and making health systems more resilient.

The LCSA calls on governments and various stakeholders in the region to initiate and accelerate a coordinated response and to define and undertake clear actions that address the challenges posed by climate change, thus ensuring healthy lives, clean environments, ecosystem services, and well-being for all South American peoples.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Dirceu Solé
E-mail: sole.dirceu@gmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Aligning Specialized Care with Primary Health Care: in search of comprehensive care for asthma patients in Brazil

Aproximando a Atenção Especializada da Atenção Primária à Saúde: em busca do cuidado integral ao paciente com asma no Brasil

Luane Marques Mello[1], Álvaro Augusto Cruz[2]

ABSTRACT

Allergic diseases and asthma are on the rise in many countries. Data show that approximately 25% of the inhabitants of industrialized countries have some type of allergy, reaching even greater proportions in developing countries. Although a national health care agenda for patients with allergies and asthma has not yet been developed in Brazil, individual initiatives in different regions have benefited thousands of patients in recent decades. The main objectives of these programs are to improve health care, quality of life (especially for patients with asthma and allergic rhinitis), and reduce disease-related morbidity and mortality indicators. To this end, these programs have been engaged in health education actions, professional training, performing active searches to ensure timely diagnosis and treatment, and providing free and continuous access to medication. However, the due to the non-institutional character of these programs, universal access, evidence-based actions, and continuity of care are not guaranteed, and it is difficult to provide comprehensive care for asthma and other allergic diseases.

Keywords: Asthma, primary health care, health care levels, comprehensive health care, allergy and immunology.

RESUMO

A ocorrência de doenças alérgicas e asma ainda cresce em muitos países. Dados mostram que aproximadamente um quarto dos habitantes de países industrializados apresenta algum tipo de alergia, e nos países em desenvolvimento estas doenças podem alcançar proporções ainda maiores da população. No Brasil, embora não exista até o momento uma agenda política nacional de atenção à saúde dos pacientes com alergias e asma, iniciativas individuais em diferentes regiões têm beneficiado milhares de pacientes ao longo das últimas décadas. Estes programas têm como principais objetivos qualificar o cuidado em saúde, melhorar a qualidade de vida (especialmente dos pacientes com asma e rinite alérgica) e reduzir os indicadores de morbimortalidade relacionados às doenças. Com essa finalidade, os programas vêm se ocupando de diversas ações de educação em saúde, capacitação profissional, busca ativa para garantir diagnóstico e tratamento oportuno, e proporcionar acesso a medicamentos de forma gratuita e continuada. Entretanto, a falta de um caráter institucional que garanta o acesso universal a ações cientificamente fundamentadas, impede a equidade e a continuidade do cuidado, além de dificultar a atenção integral em asma e em outras doenças alérgicas.

Descritores: Asma, atenção primária à saúde, atenção à saúde, assistência integral à saúde, alergia e imunologia.

1. Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Department of Social Medicine - Ribeirão Preto, SP, Brazil.
2. Fundação ProAR, Asthma Control in Bahia Program - Salvador, BA, Brazil.

Submitted Mar 07 2023, accepted June 12 2023.
Arq Asma Alerg Imunol. 2023;7(2):143-53.

http://dx.doi.org/10.5935/2526-5393.20230020-en

Illustrative clinical case

A 29-year-old man entered a Family Health Unit requesting an appointment because his asthma inhaler was no longer working. He reported that his family had recently moved to the area and he would like to be treated at this unit because he could not afford private care. He reported that there was no Family Health Unit where he used to live, and so he never had follow-up treatment. During the consultation, he reported having asthma since childhood, but the diagnosis was only confirmed when he was 18 years old. Whenever he had symptoms, he went to the emergency department and was given aerosolized medication for relief, with oral corticosteroids occasionally being prescribed for home use. He never took allergy tests, but at the time of diagnosis he underwent chest x-rays and spirometry, with normal results. He denied previous hospitalizations for asthma, but reported spending a whole day in the emergency department being medicated and waiting to get better. He reported consistently using salbutamol 1 to 2 times a month for symptom relief, but noticed progressive worsening over the last year, requiring more medication to recover for just a few hours. About 15 days ago, his cough and wheezing got worse, and he began using salbutamol at least twice a day. Performing daily activities left him increasingly tired and he woke up twice at night during this period due to symptoms. He also reported that he has not been able to play soccer with his friends each week like he used to.

During the consultation, the patient was anxious but in good general condition, afebrile, and slightly tachypneic (RR = 28 bpm, HR = 96 bpm, BP 128/89 mmHg), without intercostal indrawing or other signs of respiratory effort, with diffuse wheezing, and without difficulty speaking. His peak expiratory flow was 30% lower than predicted values for his height and age. He reported having used salbutamol twice less than 2 hours before the consultation.

At the end of the clinical evaluation, the physician confirmed that the patient's asthma was uncontrolled and untreated. He prescribed oral corticosteroids for 7 days and advised using albuterol on a daily basis. The treatment strategy was continuous anti-inflammatory action with beclomethasone spray (hydrofluoroalkane propellant), using salbutamol for symptom relief and as a rescue plan for worsening symptoms. The physician also considered it important to test lung function and allergic sensitization, for which the patient was referred to secondary care, where the tests would be requested and performed. A form was filled out describing the patient's condition and explaining the reason for the referral. Clinical reassessment was scheduled 7 days later. At the end of the consultation, the doctor informed the patient that from now on, regular follow-up visits would be scheduled and that he should feel free to return to the unit if he had any additional problems.

About the case

The case describes a young Brazilian public health system user with asthma who visited a Family Health Unit close to his new residence, a preferential access point for health services (first contact, territorialization, and regionalization of services). He was not undergoing treatment because there was no Family Health Unit in his previous neighborhood (low Family Health Strategy coverage). Since he could not pay for private health care, he never received disease control (impaired access) seeking emergency treatment when symptoms worsened (fragmented care). He sought out a Family Health Unit near his new residence, his complaints were assessed, and he was advised to wait for care (universal coverage, acceptance with risk stratification).

During the consultation, the clinical diagnosis and symptom control were evaluated, and anti-inflammatory treatment was initiated, optimizing management. Beclomethasone and salbutamol were selected because, on a local level, they are available free of charge to Primary Health Care (PHC) users. The Global Initiative for Asthma's 2021 guideline update highlights the benefits of inhaled corticosteroids and the risks of isolated use of short-acting β2-agonists, recommending a combination of inhaled corticosteroids and formoterol as a rescue medication even for mild asthma. However, it points out that the recommendations can be adapted to local circumstances, especially regarding locally available medications.[1] That is how the unit's physician proceeded. In the Brazilian public health system, other inhaled corticosteroids and long-acting bronchodilators are only available to patients who receive specialized care (a specialized form of pharmaceutical assistance in the Unified Health System). The Global Initiative against Asthma has just released a new publication aimed specifically at free primary health care systems.[2]

The patient was also referred to Allergy and Pulmonology specialties for specific tests (hierarchization and comprehensive care), since some

specialized tests are not available for PHC in the Unified Health System. At the end of the consultation, the patient received a written plan about how to proceed in case of worsening symptoms. From that point on, all his health needs would be monitored through that unit (assignment and long-term care), including the reassessment of the current condition 7 days after starting the prescribed medications. Although this is a case report, it represents the experience of thousands of patients with asthma and other allergies in Brazil, who receive a late diagnosis, fragmented care, and are waiting for a national agenda that guarantees comprehensive and universal health care wherever they are.

Comprehensive health care in Brazil

For many years, access to public health care in Brazil was guaranteed only to people who were formally employed. For the rest of the population, medical assistance was provided through direct payouts to private or charitable health services.[3] With the creation of the Unified Health System in 1989, curative and rehabilitative health care, health promotion, and disease prevention were made available indiscriminately to the entire population, meeting health needs in accordance with the principles of universality, comprehensiveness, and equity[3] (Table 1).

Since then, Brazil's morbidity and mortality indicators have changed substantially. Some authors attribute this phenomenon to better living conditions, health care quality, and accelerated change in the demographic profile of the population. The country is currently experiencing overlapping epidemiological events, a complex situation characterized by:

– goals for controlling and reducing infectious diseases, malnutrition, and reproductive health problems;
– increased mortality due to external causes;
– a concomitant increase in major chronic diseases and their risk factors (smoking, overweight and obesity, sedentary lifestyle, stress, and inadequate nutrition).[4]

To deal with this triple disease burden, PHC was defined as the health care model and the Family Health Strategy was to integrate PHC into the public health system according to World Health Organization recommendations.[5] For care to be regionalized and comprehensive, it was determined that the different components of the health system should be reorganized according to the Health Care Network (HCN) model. In this model, health professionals and patients act and transit, respectively, through a polyarchic system of services coordinated by the PHC/Family Health Strategy, to which patients must return for long-term follow-up.[6]

Comprehensive asthma care

A specific national policy to combat asthma has not yet been implemented in Brazil. Other allergic diseases, such as anaphylaxis, drug and food allergies, urticaria and angioedema are also awaiting recognition and resources. In recent years there has been a significant increase in the prevalence of allergic diseases worldwide, which has had severe social and economic consequences. Approximately 25% of people living in industrialized countries have some type of allergy. Allergic rhinitis, asthma, atopic dermatitis, chronic rhinosinusitis, allergic conjunctivitis and/or food allergy have also been affecting more and more people in low- and middle-income countries, such as Brazil, where the repercussions are even greater due to scarce resources.[7] Although hospitalizations and mortality rates are decreasing in some regions of the country, data from a recent study showed unsafe levels of symptom control (12.3%) and treatment adherence (32%) among Brazilians with asthma.[8]

Despite the lack of resources, asthma is the allergic disease that has received the greatest attention from the public authorities due to its high morbidity and mortality, recognized as unacceptable in current times. In August 2021, the Clinical Protocol and Therapeutic Guidelines for asthma were approved to regulate access to health care and asthma medications,[9] ensuring more accurate diagnosis and treatment. Recently, the Ministry of Health, through the Secretary of Primary Health Care, in partnership with the Institute for Health Technology Assessment, designed and implemented the Asthma Care Line to expand access, organize patient flow between HCN units and improve care quality, seeking to achieve comprehensive care.[10]

Two pieces of legislation have been fundamental for including asthma treatment in Brazilian public health care. The first was the Ministry of Health's National Drug Policy, which provides free access to certain asthma medications, such as beclomethasone, fenoterol, and salbutamol. This especially favored patients with milder conditions, whose symptoms,

Table 1
Fundamental and organizational principles of the Unified Health System

Unified Health System	Definition	
Fundamental principles	Universality	Health as a universal human right, guaranteeing access to health services and actions
	Comprehensiveness	Meeting all the health needs of the population: preventive, curative, and rehabilitative
	Equity	Providing services according to the needs of each community
Organizational principles	Regionalization	Distributing services and actions throughout the territory, bringing them closer to those who need them the most and making them more efficient
	Hierarchy	Providing services at increasing levels of technological complexity according to each case
	Decentralization	Redistributing decision-making power, resources, and jurisdiction among the 3 branches of government

despite being less intense, worsened often, and thus were hospitalized at the same frequency as patients with severe asthma.[11] This group benefited the most from PHC follow-up.[12] The second legislative milestone was an ordinance determining the creation of therapeutic guidelines and clinical protocols for severe asthma, creating access to medications such as budesonide, formoterol, fluticasone and salmeterol, which favored specialized treatment for these patients.[13]

A little over a decade ago, a national plan was developed for chronic diseases.[14] It has recently been updated for the next 8 years (Non-communicable Chronic Disease Plan 2021-2030), determining strategic actions regarding non-communicable diseases prevalent in the country. Cardiovascular diseases, cancer, diabetes mellitus, and chronic respiratory diseases are included in this plan, including asthma and other conditions such as chronic obstructive pulmonary disease, chronic cough, obstructive sleep apnea, dyspnea, and pulmonary nodules.[15] Despite being included in both versions of the plans, asthma was neither highlighted nor prioritized, even in the current scenario of increasing allergic diseases, an important group of chronic diseases that have been treated in a fragmented and uneven way.[16]

"The First Brazilian Consensus on Asthma Education" was published 25 years ago, the result of joint work by pulmonology, allergy, and pediatrics societies. This important initiative by medical specialties laid the foundations for asthma treatment programs, whose goals include: empowering patients with information about asthma, guiding them towards self-care and encouraging family involvement in the treatment plan; training professionals to properly treat the disease; lowering asthma morbidity and mortality indicators, while respecting the cultural, social, and economic aspects of the target population.[17]

At that time, as a result of joint effort between the newly created programs and specialty societies together with the public sector, the National Asthma Control Plan was drawn up to institutionalize assistance to patients with asthma, thus guaranteeing

access to free comprehensive care and a continuous supply of medication.[17] Although the National Asthma Control Plan was not implemented as expected, it served as a point of reference for other programs and initiatives throughout the country, which began offering specialized care for asthma and allergic rhinitis[18] (Table 2). Since then, some initiatives have been discontinued, while others have been strengthened and consolidated.[18]

Among many successful initiatives, 3 programs stand out for asthma care quality and for reducing asthma-related morbidity and mortality indicators in their regions. The Programa Criança que Chia (Wheezing Child Program) was developed in response to a study conducted in 1994 and 1995 in Belo Horizonte, MG. This study found that 64% of the evaluated children and adolescents with asthma had already been hospitalized for the condition, 71% of whom had been rehospitalized, and 90% of whom had been treated in urgent or emergency units 1 to 2 times a month for symptom relief. The results indicated that treatment was limited to the pharmacological control of worsening symptoms, predominantly on an outpatient level, as in other places. The economic impact of care was high and increasing, especially considering that the purchased supplies were, for the most part, drugs for symptom relief (fast-acting bronchodilators and methylxanthines), which are ineffective for long-term treatment.[19]

The program was made possible through an agreement between the Federal University of Minas Gerais and the Belo Horizonte Municipal Health Department, pooling public health network resources. It was first implemented in 1996, offering training to health teams and asthma education to patients and their families. It reorganized care for asthmatic children at all levels of the public health system and provided medications to treat worsening symptoms and control the disease.

The in-service training of primary care unit staff was essential for changing the care paradigm from acute crisis treatment to long-term anti-inflammatory treatment.[20] The training involved pediatricians, general practitioners, nurses, and pharmacists, and was based on the 1995 Global Initiative for Asthma document. Two referral centers for specialized care in pediatric pulmonology were created. They initially treated children < 5 years of age, since the studies showed that they are at the greatest risk of hospitalization. Children ≥ 5 years and adolescents were referred to reference centers and were later monitored by primary care units. Health education campaigns involved the health team, patients, and family members.[21] Patient attachment to a primary care unit was considered essential for continuing education about important topics, such as treatment adherence, environmental control, exposure to allergens, exercise encouragement, recognizing when symptoms are worsening.

The results of the program included greater confidence in prescribing and using inhaled corticosteroids, greater sensitivity in patient care, and greater confidence to adequately diagnose and treat the disease. In subsequent years, prescriptions for inhaled corticosteroids and the use of aerosol bronchodilator devices with spacers both increased, while hospitalizations decreased by a 79%.[22]

In an article published 10 years later, the authors reported the program's positive impact on local epidemiological indicators, quality of life, care quality, and the production of unprecedented scientific knowledge.[23] They described the following challenges: low adherence to the program (50 to 60% of children), which may have affected the asthma control results (a problem reported in other places); the fact that the municipal-university partnership depends on the will and interest of management, which could at some point make it difficult for the program to continue; increased Family Health Strategy coverage, which represents the PHC strategy in a country that, while favoring access to health care, has few professionals qualified to diagnose and treat asthma; and lack of access to more potent corticosteroids in PHC for more complex cases.[23]

Another successful example is the Bahia Asthma Control Program, which improved the lives of patients with severe asthma and related epidemiological indicators in the cities of Salvador and Feira de Santana. This multi-institutional teaching, research, and specialized assistance program, which is based on the National Asthma Control Plan, is coordinated by the Federal University of Bahia and financed by the Bahia Research Support Foundation (FAPESB) and operated with the support and collaboration of the municipal (Salvador) and state (Bahia) governments.[24] It was implemented in 2003 as a severe asthma referral center for PHC patients in the cities of Salvador and Feira de Santana and the surrounding metropolitan regions. The initiative arose from the need for an adequate treatment approach and specialized follow-up for patients with the most severe forms of asthma, most of whom do not have access to long-

Table 2
Successful asthma programs in Brazil

Asthma programs in Brazil				
Program	**Year**	**Locale**	**Objectives**	**Financing**
*Programa Criança que Chia** (Wheezing Child Program)	1996	Belo Horizonte (MG)	Team training. Asthma education. Systematization of care. Free access to medication.	Federal University of Minas Gerais Public funding: municipal and state public health network. National Medication Plan (UHS).
Programa de Atenção Integral à Criança Asmática (Comprehensive Care Program for Asthmatic Children)	1996	Fortaleza (CE)	Training in care provision. Health education. Research.	Public funding: municipal and state public health networks. National Medication Plan (UHS).
Programa de Assistência ao Paciente com Asma (Asthma Patient Assistance Program)	1996	São Luís (MA)	Creating an asthma reference center. Health education. Professional training.	Federal University of Maranhão University Hospital.
Programa Crescendo com Saúde – Infecções e Alergias Respiratórias (Growing Up Healthy Program – Respiratory Infections and Allergies)	2000	Curitiba (PR)	Organize care flow. Free access to medication. Professional training. Reducing morbidity and mortality.	Municipal health network. Federal University of Paraná Clinical Hospital and the Pequeno Príncipe Children's Hospital.
De volta para Casa & Asma (Back Home & Asthma)	2001	Porto Alegre (RS)	Training and continuing education. Guidelines and flowcharts for diagnosis and treatment. Reducing hospitalizations for asthma.	Public funding: municipal and state public health networks. National Medication Plan (UHS).
Programa de Atendimento ao Paciente Asmático do Distrito Federal (Assistance Program for Asthmatic Patients in the Federal District)	2001	Brasília (DF)	Asthma education.	Public funding: municipal and state public health networks. National Medication Plan (UHS).

Adapted from Cerci et al.[23].
UHS: Unified Health System.

Table 2 *(continuation)*
Successful asthma programs in Brazil

Asthma programs in Brazil				
Program	**Year**	**Locale**	**Objectives**	**Financing**
Programa Respira Londrina (Breathe Londrina Program)	2002	Londrina (PR)	Continuing education. Active patient search. Timely diagnosis and treatment. Free access to medication and comprehensive care.	Public funding: municipal and state public health networks. National Medication Plan (UHS).
Programa de Controle da Asma na Bahia – ProAR** (Bahia Asthma Control Program – ProAR)	2003	Salvador e Feira de Santana (BA)	Comprehensive care. Free access to medication. Creating a severe asthma reference center. Health education. Professional training.	Bahia State Research Support Foundation (FAPESB). Public funding: municipal and state public health networks. National Medication Plan (UHS).
Programa de Controle da Asma – CATAVENTO (CATAVENTO Asthma Control Program)	2003	Goiânia (GO)	Continuing education. Active patient search. Free access to medication. Care training. Awareness and improvement of local epidemiological indicators.	Public funding: municipal and state public health networks. National Medication Plan (UHS).
Programa de controle de Asma – Respira Niterói (Asthma Control Program – Breathe Niterói)	2003	Niterói (RJ)	Diagnosis and treatment. Comprehensive care. Public management awareness. Improving local epidemiological indicators.	Public funding: municipal and state public health networks. National Medication Plan (UHS).
Plano de Atenção ao paciente com asma e rinite do Município do Rio de Janeiro – RespiraRio (Care Plan for patients with asthma and rhinitis in the city of Rio de Janeiro – RespiraRio)	2004	Rio de Janeiro (RJ)	Reducing morbidity and mortality. Professional training. Continuing education. Creating asthma reference centers. Ensuring access to medication and diagnostic tests. Improving the information system.	Public funding: municipal and state public health networks. National Medication Plan (UHS).

Adapted from Cerci et al.[23].
UHS: Unified Health System.

Table 2 *(continuation)*
Successful asthma programs in Brazil

Asthma programs in Brazil				
Program	**Year**	**Locale**	**Objectives**	**Financing**
Programa CreAs – Controle de Rinite e Asma da Santa Casa de Misericórdia (Rhinitis and Asthma Control Program of Santa Casa de Misericórdia)	2006	Vitória (ES)	Establish a reference center. Health education. Continuing education. Searching for and controlling comorbidities.	Municipal funding, Santa Casa de Misericórdia School of Medicine Teaching Hospital (EMESCAM).
Programa Infantil de Prevenção de Asma (PIPA) (Children's Asthma Prevention Program)	2012	Uruguaiana (RS)	Reducing morbidity and mortality from asthma in children.	Public funding: Municipal Secretary of Health, municipal government.

Adapted from Cerci et al.[23].
UHS: Unified Health System.

term anti-inflammatory treatment.[24,25] The program's main goals were to provide comprehensive care for patients with asthma in the public health system, to provide free asthma medications, to construct reference outpatient clinics for severe cases, and to train primary care teams to treat mild and moderate forms of the disease.

In the first years of the program, 4 reference centers were established in Salvador and 1 in Feira de Santana, expanding access to specialized asthma care. After initiating the program, there was an 85% reduction in emergency room visits, a 90% reduction in hospitalizations in the public health system, an 86% reduction in school and work absenteeism, and a 67% decrease in oral corticosteroid use in the target population.[26]

Regarding the disease's direct and indirect costs to families, there was a 50% reduction in commuting time, a 59% reduction in time spent in waiting rooms due to asthma crises, and an 80% reduction in school absenteeism. Although pharmaceuticals weighed heavily on family budgets, after the program began, asthma-related expenses reduced from 37.5% to 4.5% of the family income. As a result, the mean family income increased 10% and treatment costs reduced 86.3%, resulting in a 50% mean increase in annual family income.[27] The cost of hospitalizations and emergency/intensive care was significantly reduced, even considering the increased public sector spending on inhaled medications, complementary tests, and consultations.[28]

Since the program's implementation, a number of studies based on its data have produced highly relevant results. One of these studies compared demographic, clinical, and pulmonary function profiles between 2 cohorts of adults with severe asthma: a Brazilian cohort from the Bahia Asthma Control Program, a European cohort from a consortium of academic institutions, the pharmaceutical industry, and patient organizations (U-BIOPRED), and controls with mild/moderate asthma from Brazil and 11 European countries. Despite some differences, the phenotypic similarities confirmed asthma as a nosological entity, which allows cooperative studies between groups from

different regions of the world on important issues, such as the phenotypic variability of the disease and treatment response.[29]

Another study conducted with the Bahia Asthma Control Program cohort found that patients with severe asthma are 53% more likely to be depressed, possibly due to poor quality of life from frequent crises and disabling symptoms. The study considered asthma an adverse life event, inducing suffering and stress (both physical and mental). Psychological stress can lead to an increase in pro-inflammatory markers, which may underlie the relationship between asthma and depression.[30]

The Children's Asthma Prevention Program, created in 2012 in Uruguaiana, RS, is another successful example that began as an individual initiative and was later incorporated as a municipal program, ensuring that its actions reached the entire municipality on a continuing basis. Aiming to reduce morbidity and mortality, it decisively improved care quality, epidemiological indicators, and the quality of life of children and adolescents with asthma in the region.[31]

Where are we right now?

According to the World Health Organization, 400 million people worldwide are without access to essential health care. Although significant advances have been made in health conditions and quality of life, they are unevenly distributed, both among and within countries. In some places, health systems are weak and poorly integrated, staff and resources are lacking, and the provided care is fragmented and of low quality.[32] It is believed that integrated health services focused on continuous care in a user-centered approach will lead to better care quality, increased resolution of health conditions, and greater user satisfaction while optimizing resources.[32,33]

Aligning specialized care at secondary and tertiary levels with PHC is foundational to comprehensive health care (aka "shared" or "collaborative" care), which is centered on staff routines and greater involvement of care teams and health services at different levels of care.[34] Similar efforts have shown positive results in asthma treatment,[35] as well as in other areas, such as mental health[36] and ophthalmology.[37]

Specialized care, an important component of the Brazilian health system, is the most precarious level due to a lack of coordination and overload, making it difficult to organize health care according to HCN parameters.[5] Certain aspects of HCN organization, especially PHC and specialized care, have been the subject of frequent discussion. The following have been identified as critical points for restructuring efforts:

1. the lack of understanding about how HCNs work and the role of each component in their organization;
2. the lack of coordination within the HCN, which, by definition, should control PHC;
3. the lack of a referral system based on risk classification, guaranteeing equitable care;
4. the lack of qualified multidisciplinary teams for comprehensive and integrated specialized care;
5. non-cost-effective diagnostic services recommended apart from scientific evidence that are not prioritized according to risk.

Underdiagnosis and suboptimal care for asthma also occur in other countries, especially those with limited health resources. A Vietnamese study proposed an algorithm based on syndromic diagnosis to address respiratory complaints in health units, finding greater diagnostic standardization and more appropriate therapeutic regimens started in a timely manner.[38]

Perhaps an international effort to promote greater awareness and prioritization of asthma and other allergic diseases in public health systems could change the current treatment situation and improve patient quality of life.

Final considerations

Brazil still has no national policy for people with allergic diseases and asthma. The advances and benefits obtained so far result from localized efforts that have improved the lives of thousands of patients with asthma and local epidemiological indicators. These pioneer programs serve as models to be reproduced and adapted in order to reach more people and yield greater results. While acknowledging the invaluable role of these initiatives for quality asthma care, their heterogeneous distribution is contrary to the Unified Health System's principles of equity and comprehensiveness.

Understanding the Brazilian health system's functioning, organization, and the role of each service point in the HCN are fundamental for identifying

weaknesses and finding solutions. Closer alignment between care levels is foundational for diagnosis, evidence-based treatment, risk stratification, and regulating patient flow within the HCN, including necessary adaptations to improve care quality, health conditions, and the population's quality of life. Better training for agents at each care level (not just PHC) can be the starting point for this change. Each level of health care should be aware of the skills and scope of the others, so that health system users receive care in a climate of solidary cooperation.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Luane Marques Mello
E-mail: luane@fmrp.usp.br

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Olfactory dysfunction: a narrative review from diagnosis to treatment

Distúrbios do olfato, uma revisão narrativa do diagnóstico ao tratamento

Laís Lourenção Garcia da Cunha[1], Sarah Aguiar Nunes[1], Adriana Pitchon[1], Andressa Mariane da Silva[1], Jorge Kalil[1], Clóvis Eduardo Santos Galvão[1], Fábio Fernandes Morato Castro[1]

ABSTRACT

Olfactory dysfunction significantly impacts quality of life, and allergists and clinical immunologists must be informed about it for diagnostic and interventional purposes. The causes are varied: allergic rhinitis, chronic rhinosinusitis with or without polyps, upper airway infections, exposure to chemicals, neurological diseases, drugs, trauma, and aging itself. Olfactory function can be evaluated and measured by several tests that use different methodologies to evaluate and identify odors, olfactory threshold, and olfactory discrimination. These tests are fundamental for objectively characterizing patient complaints and evaluating olfactory function before and after therapeutic interventions. Olfactory disorders are treated according to their etiology, so determining their cause is a major factor in treatment efficacy. The main options include topical corticosteroids, which have a significant impact on patients with sinus disease, olfactory training, other therapies (such as omega 3 and intranasal vitamin A), in addition to therapies that require further research.

Keywords: Rhinitis, olfactory dysfunction, anosmia, sinusitis, COVID-19.

RESUMO

Os distúrbios do olfato (DO) impactam de forma significativa na qualidade de vida dos indivíduos, e o conhecimento teórico a respeito do assunto deve ser de domínio dos alergologistas e imunologistas clínicos, possibilitando, assim, o seu diagnóstico e implementação de intervenções. Suas causas podem ser variadas, entre elas estão: rinite alérgica, rinossinusite crônica com ou sem pólipos, infecções de vias aéreas superiores, exposição a substâncias químicas, doenças neurológicas, drogas, traumas e o próprio envelhecimento. O olfato pode ser avaliado e mensurado através de testes com metodologias diferentes, cujo objetivo é avaliar parâmetros como a identificação de odores, limiar e discriminação olfativa. Esses testes são de fundamental importância para caracterizar objetivamente a queixa do paciente, como também avaliar o olfato antes e após determinada aplicação terapêutica. O tratamento das desordens olfativas é baseado em sua etiologia, portanto determinar a sua causa é indispensável para uma melhor eficácia no manejo. Entre as principais opções estão os corticoides tópicos, com impacto significativo nos pacientes com doença sinusal associada, treinamento olfatório e outras intervenções como ômega 3, vitamina A intranasal, e terapias que ainda requerem mais estudos.

Descritores: Rinite, transtornos do olfato, sinusite, anosmia, COVID-19.

Introduction

Olfactory and taste disorders were frequently reported during the SARS-CoV-2 pandemic. Approximately 30% of infected individuals had some level of olfactory deficit[1,2]. Thus, a symptom heretofore little studied became the focus of clinical studies and part of the daily routine in doctors' offices.

Olfaction plays an important social role by providing information about the environment. Decreased or

1. Faculdade de Medicina da Universidade de São Paulo, Clinical Immunology and Allergy Service of Hospital das Clínicas - São Paulo, SP, Brazil.

Submitted Sept 27 2022, accepted Mar 07 2023.

Arq Asma Alerg Imunol. 2023;7(2):154-62.

http://dx.doi.org/10.5935/2526-5393.20230021-en

absent olfaction interferes significantly in personal and social functions, consequently decreasing quality of life due to reduced sense of taste, loss of pleasure from eating, weight loss, increased risk of eating spoiled food, difficulty recognizing toxic chemical substances, and interference with interpersonal relationships[3,4].

Allergic rhinitis is among the most common nasosinusal conditions seen by allergy specialists and clinical immunologists, affecting approximately 10 to 25% of the world's population. Although the most common symptoms, such as nasal obstruction, rhinorrhea, sneezing, and itching are well recognized and addressed in clinical practice, olfactory disorders (OD) and taste disorders can also be present in these patients, with an estimated prevalence of 23% to 31%[5,6]. Thus, this review was conducted to describe the pathophysiology of olfaction, its causes, diagnostic tools, and olfactory disorder treatments.

Methods

For this narrative literature review, LILACS, MEDLINE, and SciELO were searched between May and August 2022 for studies including the following descriptors: rhinitis, sinusitis, COVID-19, olfactory disorders, sinusitis and anosmia. Full-text articles in Portuguese, English, or Spanish published in the last 20 years (2002 to 2022) were eligible for inclusion. The titles and abstracts were reviewed and analyzed, with preference given to systematic reviews, meta-analyses, and randomized controlled trials. After title and abstract reading, 45 studies were selected for full text reading and analysis, of which 35 were included: 2 were included despite predating the publication range (1982 and 1997) and 1 relevant book chapter was also included.

Pathophysiology

Adequate olfactory function depends on several factors, such as appropriate stimulus to receptors in the nasal mucosa, the reception, transmission, and processing of information by the olfactory bulb, the olfactory cortex, and components of the limbic system[7].

The olfactory mucosa is located in the upper nasal cavity, covering part of the septum, cribriform plate, and superior turbinate; it measures approximately 2 cm² and is usually covered by mucus. Pseudostratified columnar epithelium consists of 4 main cell types,[4,7,8] as described below.

– *Olfactory sensory neurons:* bipolar cells that connect the epithelial surface with the olfactory bulb.

– *Support cells:* provide support for sensory neurons and for the detoxification and phagocytosis of substances to which the olfactory epithelium is exposed.

– *Basal layer cells:* small cells responsible for maintaining the balance between apoptosis and neogenesis, differentiating to replace injured olfactory sensory neurons or support cells.

– *Microvillar cells:* function still unknown.

Odors produce a stimulus, whose path passes through the paleocortex, the oldest part of the brain, triggering emotions and producing memories. Olfactory perception is influenced by emotion, and unpleasant odors, which can provoke a sense of alert or danger, are perceived more quickly than pleasant ones, even increasing the heart rate.[4]

Olfactory disorders

Olfactory disorders can be classified as quantitative or qualitative. Quantitative disorders include hyposmia (reduced olfactory function) and anosmia (no olfactory function). Qualitative disorders are subdivided into parosmia (distorted perception of an odorant) and phantosmia (perception of an odor that is not present) (Table 1).[4]

Causes of olfactory dysfunction

Exposure to chemical substances, pollution, neurological diseases, drugs, trauma, aging, and nutritional disorders can lead to OD (Table 2). However, two-thirds of ODs are caused by upper respiratory tract infections or paranasal sinus diseases.

Rhinitis

Little is currently known about olfactory alterations in rhinitis, especially allergic rhinitis. It is assumed to be a mixed mechanism involving inflammatory and physical changes.[9] Among inflammatory alterations, Guilemany et al. identified 2 important

Table 1
Classification of olfactory disorders

Olfactory disorders	
Quantitative	**Qualitative**
Hyposmia	Parosmia
Anosmia	Phantosmia

markers: peripheral eosinophilia and eosinophilic cationic protein in the nasal mucosa. They also found a correlation between olfaction and persistent allergen exposure: in perineal allergic rhinitis involving continuous exposure to mites, there could also be persistent hyposmia, while in seasonal allergic rhinitis, hyposmia occurs only during natural exposure to pollens.

This remarkable observation could be because the late phase of allergic reactions is characterized by eosinophilic granulocytes and humoral and cellular alterations in the nasal mucosa, which was more frequent in patients with perennial allergic rhinitis than seasonal rhinitis. It has been inferred that chronic inflammation reduces the flow of information through the olfactory receptors, thus reducing olfactory detection. Hence, allergen type and inflammation duration trigger different mechanisms.[1] In addition to clarifying this mechanism, Passali et al. found that OD was more severe in patients with allergic rhinitis than in those with non-allergic rhinitis.[9,10]

Another study analyzed the epithelium of the nasal mucosa in mice with allergic rhinitis sensitized and chronically exposed to fungi. Significant thinning was observed in the olfactory epithelium, in addition to apoptotic markers and numerous eosinophilic infiltrates. It is speculated that apoptosis is mediated by tumor necrosis factor and interferon, like the pathophysiology of asthma. In this model, increased tumor necrosis factor was directly associated with apoptosis of olfactory neurons.[11]

Table 2
Causes of olfactory disorders

Chemical agents
Pollution
Neurological diseases
Drugs
Nutritional disorders
Upper respiratory tract infections
Nasosinusal diseases
Trauma
Tumors
Aging
Kallmann syndrome

It is also believed that the physical mechanism plays an important role in OD, since nasal obstruction also impedes the transport of odor particles to the olfactory epithelium.[9] Nasal obstruction is mainly due to hypertrophy of the mucosa of the lower, middle and/or upper turbinates, or through the formation of polyps as a result of a degenerative process caused by poorly controlled allergic rhinitis.[12]

Chronic rhinosinusitis

The prevalence of chronic rhinosinusitis (inflammation of the mucosa and paranasal sinuses > 12 weeks) is 10% among adults in Europe and the USA and 5.5% in Brazil. The symptoms include facial pain, nasal secretion, congestion, and hyposmia or anosmia. Olfactory changes occur in 30.0% to 78.2% of patients, varying according to age, sex, and the presence of polyps.[13]

The disease has 2 main phenotypes: chronic rhinosinusitis with and without nasal polyposis (CRSwNP and CRSwoNP, respectively).[13] The pathophysiology of chronic rhinosinusitis goes far beyond impaired ventilation and sinus cavity drainage. Current conceptualization involves immunology of the nasosinusal mucosa, including deviation of inflammatory signatures (type 1, 2 and/or 3), in which each determines the endotype of chronic rhinosinusitis, the severity of the disease, prognosis, and treatment response.[13]

Soler et al. investigated inflammatory proteins in the mucus of the olfactory slit in patients with CRSwNP and CRSwoNP. The olfactory changes in these patients were documented using the Sniffin' Sticks test (Burgardt, Wedel, Germany). No difference was observed between the CRSwNP and CRSwoNP groups in terms of risk factors that interfere with olfaction: age, sex, asthma, allergic rhinitis, diabetes mellitus, depression, and smoking. However, an inverse relationship was observed between olfaction and chemokines CCL2 and CCL3, cytokines IL5, IL6, IL13, IL10, IL9 and IL23, and total IgE. However, high levels of VEGF-A and CXCL5 have been associated with better olfactory performance. All of these proteins were higher in the CRSwNP group except VEGF-A,[14] which would explain why patients with CRSwNP have lower olfactory performance.

In addition to histological analysis, this study also assessed the degree of olfactory fossa opacification in computed tomography, finding that the greater the opacification, the greater the presence of proteins harmful to olfaction.[14] In addition, CRSwNP can mechanically obstruct the olfactory epithelium through polyp formation, leading to greater impairment than CRSwoNP. Aspirin-exacerbated respiratory disease stood out in the CRSwNP group, with olfactory impairment occurring in up to 72% of the patients.[14]

Upper airway infections

Upper airway infections, which are responsible for 18% to 45% of olfactory dysfunction cases, can have a gradual onset and are more frequent in women aged 40 to 50 years. Other significant causes include respiratory infections with rhinovirus, adenovirus, and coronavirus. Symptoms usually improve spontaneously within 3 months of infection.[15]

OD cases increased during the COVID-19 pandemic, highlighting the importance of this cause. It is speculated that in 2020, 35% to 85% of patients with COVID-19 also had OD and, of these, 10% to 17% did not spontaneously improve. Unlike OD due to other viruses, these patients had sudden changes in taste perception.[15] The mechanism of action is still uncertain, involving physical aspects, mucosal edema, and mucus, which prevent particle-bound compounds from reaching the olfactory slit. In addition, the inflammatory aspect of SARS-CoV-2 infection, the release of mediators such as tumor necrosis factor-alpha, IL1-alpha and IL1-beta, in addition to neurotropism and the involvement of support cells in the olfactory epithelium, may also explain the rapid clinical course and worse prognosis of OD in SARS-CoV-2 than other respiratory viruses.[15,16]

Trauma

Trauma, which may cause 8% to 20% of OD cases, is usually head trauma. Loss of olfaction often occurs immediately, although some patients may take months to notice. Hyposmia occurs more in frontal lesions, while anosmia is 5 times more prevalent in occipital lesions. In such cases, odor discrimination may be more impaired than odor identification.[2]

Toxins/inhaled drugs

Drugs such as amphetamines, antibiotics, and antihypertensives can affect olfaction reversibly or

irreversibly. Heavy metals or toxic gases such as nicotine, carbon monoxide, and solvents can lead to OD in 2% to 6% of exposed individuals. Since the work environment can be the source of exposure (occupational disease), the use of personal protective equipment should be reinforced and OD should monitored through olfactory tests.[2]

Syndromes

Syndromes lead to a small number of OD cases (≤ 4%). Kallmann syndrome is the best known of these, presenting clinical signs such as hypogonadotropic hypogonadism, infertility, and hyposmia/anosmia.[2]

Aging

The olfactory threshold progressively reduces with aging, which can directly affect nutrition in older adults by reducing pleasure from eating. It can negatively affect cognition and can be the initial symptom in dementia syndromes such as Alzheimer's disease and Parkinson's disease.[17]

Tumors and neoplasms

Tumors, such as olfactory groove meningioma, esthesioneuroblastoma, and hamartoma, may be related to olfactory dysfunction and require assessment through imaging tests, especially brain magnetic resonance imaging.[2]

Olfactory assessment methods

Olfaction can be assessed through several tests, each with different characteristics and standardized for a target population. Some of these include Sniffin' Sticks, which are widely used in Europe, and the University of Pennsylvania Smell Identification Test and the Connecticut Chemosensory Clinical Research Center olfaction test, which are widely used in the USA.

These tests evaluate olfactory identification, threshold, and discrimination through different methods. They are of fundamental importance for objectively characterizing patient complaints and are useful for assessing olfaction before and after therapeutic interventions.

University of Pennsylvania Smell Identification Test

This test, which only assesses olfactory identification, is easy to apply and can be performed by the patient at home. It contains 40 scratch-and-sniff items that patients identify from a list of responses. Total scores classify patients as normosmic, hyposmic, or anosmic. This test has been validated for use in Brazil.[18]

Connecticut Chemosensory Clinical Research Center odor identification test

This test assesses not only odor identification, but the olfactory threshold, adding further information to the final evaluation, which is derived from the sum and average scores of each test.

In the identification test, the examiner opens an unlabeled bottle that the patient smells and identifies from a list of possible responses. N-butanol is presented at different concentrations compared to a bottle of distilled water. The patient decides which bottle has an odor and, after consecutive responses, the patient's olfactory threshold is determined. This test has also been validated for use in Brazil.[19]

Sniffin' Sticks test

Sniffin' Sticks is a more complete test that takes longer to apply. It assesses odor threshold, discrimination, and identification. In its 3 steps, which can be applied separately, the patient smells pen-like odor-dispensing devices (sticks).[20]

To assess odor threshold, the patient must choose between 3 sticks, one of which contains n-butanol diluent and the other 2 are odorless. The 16 sets of odorants contain increasing diluent concentrations, and the test is reapplied at each successful response to avoid random identification. The threshold is determined by the mean concentration of the last 4 successful responses. Odor discrimination is tested by distinguishing between 3 sticks: 2 of which have the same odor. Sixteen sets are presented, and the score is the sum of the successful responses. In the identification stage, a series of 16 sticks are presented to the patient, who must identify the corresponding odor from a list of 4 responses. This stage is still being validated for use in Brazil.

Treatments

Since olfactory disorders are treated according to their etiology, determining the cause of the dysfunction is essential for more effective treatment.[21]

Glucocorticoids

Topical corticosteroids are widely used for olfactory disorders, regardless of etiology. They have a significant impact on patients with chronic rhinosinusitis, whereas in other etiologies they require further study. Nevertheless, due to the low risk of side effects, they can be used as monotherapy or in association with other treatments.[21] For SARS-CoV-2-related OD, if they were previously taken for allergic rhinitis or chronic rhinosinusitis, their continued use is recommended.[22]

Although topical corticosteroids seem to assist in recovery after SARS-CoV-2-related OD, their effectiveness must be carefully evaluated, given that one-third of these patients partially or completely recover spontaneously. Since there is no well-established scientific evidence about the benefit of topical corticosteroids for post-infection anosmia, no recommendations have been made regarding their routine use.[22]

It should be pointed out that nasal corticosteroid spray only partially reaches the olfactory cleft, so some studies have used techniques involving a long applicator or nasal wash with a high volume of saline solution associated with diluted corticosteroids (fluticasone or budesonide).[23]

High-volume nasal budesonide has been used for OD in chronic rhinosinusitis, with proven safety in short term treatment (4-8 weeks). Regarding side effects and possible changes in the hypothalamic-pituitary-adrenal axis, Smith et al. evaluated the safety of long-term high-volume nasal corticosteroid use in adults with chronic rhinosinusitis who had previously undergone endoscopic sinus surgery. High-volume irrigation with 1 mg nasal budesonide was performed at least twice a day for an average of 38.2 months (patients who had recently used systemic corticosteroids were excluded). The authors failed to find evidence that the hypothalamic-pituitary-adrenal axis had been suppressed by > 2-year courses of daily high-volume nasal budesonide irrigation.[24]

The benefits of systemic corticosteroids in OD include reducing inflammatory mediators and influencing expression of the olfactory gene. Systemic corticosteroids should be used with caution due to their side effects and the lack of evidence.[24] Some studies have shown benefits for short-term use after COVID-19. Disease duration, age, sex, and parosmia were unrelated to corticosteroid treatment response.[22]

Sodium citrate

A study found that intranasal sodium citrate led to better odor identification scores in patients with post-infection hyposmia than placebo, but there was no significant change in patients with hyposmia of other etiologies, such as trauma, nasosinusal, or idiopathic disease. Since calcium has an inhibitory role in olfactory signal transduction, it is believed that improvement is due to the action of sodium citrate in reducing the intracellular calcium influx, leading to reduced free calcium in the nasal mucus layer.[25]

Another randomized, double-blind study assessed the therapeutic and side effects of sodium citrate. The effects were transitory, peaking 30 to 60 minutes after application, with mild adverse effects: oropharyngeal pain, nasal paresthesia, mild rhinorrhea, and itching.[26] However, these findings were limited and had a low evidence level when replicated in a larger study. Nevertheless, it was effective for phantosmia.[27]

Alpha-lipoic acid

It is believed that due to the release of growth factor and antioxidant effects, alpha-lipoic acid can be used to treat post-upper respiratory tract infection OD, leading to olfactory receptor regeneration. In one study, 23 patients with olfactory loss for a mean of 14 months who received oral alpha-lipoic acid (600 mg/day) for 4.5 months showed improved olfactory function, with young people having better olfactory recovery than those > 60 years of age. Although the main reported side effect was gastric intolerance, further research is still needed.[28]

Vitamin A

Vitamin A can help treat post-infectious olfactory loss due to its role in the regeneration of olfactory neuronal receptors; its topical use has been linked to good results and has been increasingly studied.

A retrospective study of 170 patients assessed the efficacy of vitamin A in patients with post-infection and post-traumatic olfactory disorders: 46 patients were treated with 12 weeks of olfactory training, while the remaining 124 received olfactory training and topical vitamin A 10,000 IU/day for 8 weeks. The Sniffin' Sticks test was performed after 10 months. Olfaction improved in 37% of the vitamin A group and 23% of the control group. In addition to showing that vitamin A plus olfactory training had greater benefits than training alone, it was concluded that topical Vitamin A is a viable treatment option for post-infection OD, although further research is needed.[29]

Omega-3

In a prospective, non-blinded study of 58 patients with post-infection OD, omega 3 supplements plus olfactory training proved more beneficial than olfactory training alone. Age, sex, and symptom duration had no influence on any of the groups.[30]

Another randomized, prospective study evaluated omega-3 supplementation in patients with olfactory disorders after endoscopic resection of a skull base tumor. The patients in this study were divided into a group that underwent nasal lavage with saline solution plus omega-3 supplementation and a control group that underwent nasal lavage with saline solution only. The omega-3 supplementation group had fewer persistent olfactory disorders than the control group, which may be due to its effects on olfactory neuron healing and regeneration.[31] Due to its low potential for side effects, it might be useful as a therapy for some types of OD, although further research is required.

Olfactory training

The pathophysiological mechanism involved in olfactory training is still unclear. It is believed that repeated exposure to pungent odors can promote the regenerative capacity of olfactory neurons and improve their function.[22,32] The effectiveness of this treatment was clearly established in a recent meta-analysis, even for OD etiologies with worse prognosis, such as traumatic brain injury.[33]

Patients should undergo training twice a day for an average of 12 weeks, smelling 4 pungent odors (phenyl ethyl alcohol [rose], eucalyptol [eucalyptus], citronellal [lemon], and eugenol [clove]). Training must occur in a quiet place, with the patient concentrating on the odor for 20-30 seconds. Increasing the treatment duration up to 56 weeks and changing the odors can increase the treatment's effectiveness.[22,33] After 12 weeks of training in patients with post-infectious anosmia, a study found neural reorganization in functional magnetic resonance imaging.[32]

Surgical treatment

Since one cause of OD could be that odor molecules are prevented from reaching the olfactory cleft, certain anatomical alterations, such as deviated septum, turbinate hypertrophy, and concha bullosa might have a great impact on olfaction and should be surgically evaluated and corrected.[2]

Immunobiologicals

Patients with chronic rhinosinusitis with nasal polyposis have responded well to biological drugs, such as dupilumab, omalizumab, and mepolizumab, despite their limited applicability due to high cost and indication criteria. Their use is still restricted, with formal indication limited to chronic rhinosinusitis-related OD.[34-36]

Conclusions

ODs have a great socioeconomic impact. Their etiologies and treatment are the focus of increasing research due to significantly increased prevalence with the SARS-CoV-2 pandemic. It is important for specialists to understand the involved anatomy and the phenotypes and endotypes of OD related to nasosinusal diseases, as well as the impact of the cytokines related to each immunological profile. Efforts to expand diagnostic testing to objectively assess olfaction are equally important, since it is the only way to correctly monitor and diagnose OD.

Alternative therapies, such as olfactory training, should also be further investigated, since they could stimulate olfactory neuron regeneration, improve olfactory function, and are consistently recommended. Studies are still needed to validate other promising therapeutic options, such as omega 3, alpha-lipoic acid, intranasal citrate, and intranasal vitamin A.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Laís Lourenção Garcia da Cunha
E-mail: laislgc@gmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Drug reaction with eosinophilia and systemic symptoms (DRESS): a diagnostic and treatment challenge

Reação a drogas com eosinofilia e sintomas sistêmicos (DRESS): desafio no diagnóstico e tratamento

Dina Larissa Capelasso da Costa[1], Débora Mutti de Almeida Monteiro[1], Thábata Chiconini Faria[1], Ana Flavia Faria de Camargos[1], Veridiana Aun Rufino Pereira[1], Maria Elisa Bertocco Andrade[1], Fátima Rodrigues Fernandes[1]

ABSTRACT

Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a serious disease. Its severity is related to the degree of visceral involvement and its mortality rate is approximately 10%. Diagnosis is a challenge, although RegiSCAR scores can facilitate the process. **Objective:** To analyze clinical and laboratory data, clinical course, and classify cases according to RegiSCAR scores among patients diagnosed with DRESS who were admitted to the Allergy and Immunology service of the Hospital do Servidor Público Estadual de São Paulo. **Method:** This retrospective study analyzed the medical records of patients seen between January 2006 and January 2020. **Results:** There was a higher prevalence of women, with DRESS mainly affecting adults and older adults; cardiovascular diseases were the most frequent comorbidity. The most common clinical symptom was fever (69.2%), while the most common laboratory finding was eosinophilia. The most frequent skin lesion was maculopapular rash, and anticonvulsants were the main prescribed drug class. The drug was used for a mean of 2.1 weeks, and all patients received systemic corticosteroids as the main treatment. Human immunoglobulin was used as an additional treatment in 3 patients. Mortality was 7% in the acute phase and 14% due to secondary causes. **Conclusion:** DRESS is a severe, complex, and potentially fatal syndrome whose diagnosis is challenging. RegiSCAR scores helped confirm diagnosis and differentiate it from other diseases. The disease's mortality highlights its severity. Recognizing and excluding the implicated drug and initiating early treatment led to a greater chance of survival for these patients.

Keywords: Eosinophilia, anticonvulsivants, drug hypersensitivity, drug hypersensitivity syndrome.

RESUMO

Introdução: A reação a medicamentos com eosinofilia e sintomas sistêmicos (DRESS) trata-se de uma doença grave, sendo sua gravidade relacionada ao grau de acometimento visceral, e sua taxa de mortalidade de cerca de 10%. Seu diagnóstico é desafiador, e a utilização do escore RegiSCAR como ferramenta facilita a formação deste diagnóstico. **Objetivo:** Analisar os aspectos clínicos, laboratoriais, evolução e classificação dos casos segundo o RegiSCAR dos pacientes internados no serviço de Alergia e Imunologia do Hospital do Servidor Público Estadual de São Paulo, com o diagnóstico de DRESS. **Método:** Trata-se de um estudo retrospectivo baseado na análise de prontuários de pacientes atendidos no período entre janeiro de 2006 a janeiro de 2020. **Resultados:** Neste estudo verificou-se maior prevalência do sexo feminino, e a DRESS acometeu principalmente adultos e idosos, tendo como comorbidades mais frequentes as doenças cardiovasculares. Dos sintomas clínicos, 69,2% dos pacientes apresentava febre, e a alteração laboratorial mais encontrada foi a presença de eosinofilia. A lesão cutânea mais frequente foi o exantema maculopapular, e os medicamentos, os anticonvulsivantes. O tempo prévio de uso do medicamento foi de 2,1 semanas, e todos os pacientes receberam corticoide sistêmico como tratamento principal, e 3 pacientes fizeram uso da imunoglubulina humana como tratamento adicional. A mortalidade foi de 7% na fase aguda, e 14% por causas secundárias. **Conclusão:** A DRESS é uma síndrome complexa grave e potencialmente fatal, cujo diagnóstico é desafiador. O uso do escore preconizado pelo RegiSCAR demonstrou ser importante auxílio na confirmação do diagnóstico e na diferenciação de outras doenças. A mortalidade encontrada destaca a gravidade da doença. Reconhecer e excluir a droga implicada e iniciar um tratamento precoce permite maior chance de sobrevida para estes pacientes.

Descritores: Eosinofilia, anticonvulsivantes, hipersensibilidade a drogas, síndrome de hipersensibilidade a medicamentos.

1. Hospital do Servidor Público Estadual de São Paulo, Allergy and Immunology Fellowship Program - São Paulo, SP, Brazil.

Submitted Apr 29 2023, accepted June 28 2023.

Arq Asma Alerg Imunol. 2023;7(2):163-70.

http://dx.doi.org/10.5935/2526-5393.20230022-en

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe type of cutaneous adverse drug reaction characterized by rash, fever, leukocytosis with eosinophilia and/or atypical lymphocytes, lymph node enlargement, and renal and/or hepatic dysfunction. Its incidence is 1 in 1,000 to 1 in 10,000 drug exposures.[1,2] DRESS severity is often related to the degree of visceral involvement and its mortality, which has a rate of 10%. Identifying the condition early to start specific treatment as soon as possible is of utmost importance.[3]

The pathogenesis of DRESS is only partially understood and involves different mechanisms, such as detoxification defects leading to reactive metabolite formation and subsequent immunological reactions, slow acetylation, and reactivation of human herpes.[4]

Symptom onset typically occurs after 2 weeks of medication use. Clinical characteristics of the disease include multiorgan involvement and often signs of clinical worsening such as fever, rash, and renal and hepatic dysfunction, occurring even after discontinuation of the medication.[4,5] Anticonvulsants and allopurinol are the most common causes of DRESS, and the main treatment consists of withdrawing the offending medication and starting systemic corticosteroids.[66]

Diagnosis is challenging, as the different signs and symptoms of DRESS are also observed in other serious conditions with similar characteristics. Therefore, an international study group called RegiSCAR developed a score based on patients' clinical condition and additional laboratory/histopathological data that classifies the diagnosis of DRESS as definitive, probable, possible, or negative (Table 1).[2,4,6]

Table 1
RegiSCAR criteria for potential DRESS cases

(1) Hospitalization
(2) Reaction suspected to be drug-related
(3) Acute rash
(4) Fever > 38 °C
(5) Enlarged lymph nodes involving at least 2 sites
(6) Involvement of at least 1 internal organ
(7) Blood count abnormalities – Lymphocytes above or below reference intervals – Eosinophils above references intervals – Platelet count below reference intervals

DRESS = drug reaction with eosinophilia and systemic symptoms.
RegiSCAR = registry of severe cutaneous adverse reactions.
Fonte: Kardaun SH, et al.[4].

Objective

This study aimed to assess clinical and laboratory data, as well as the evolution and classification of patients with suspected DRESS admitted to the Allergy and Immunology service of the Hospital do Servidor Público Estadual de São Paulo, Brazil, according to the RegiSCAR criteria.

Population and methods

This was an observational, descriptive, retrospective, and prospective study with data from patient records and databases. Patients with suspected DRESS who were classified as possible, probable, or definitive DRESS according to the RegiSCAR score treated at Hospital do Servidor Público Estadual de São Paulo – Francisco Morato de Oliveira from January 2006 to January 2020 were included in the study. There was no age restriction. Patients were analyzed according to age, sex, suspected drug, presence of fever, peripheral eosinophilia (> 500), presence of atypical lymphocytes, involvement of other systems, skin manifestations, treatment, complications/sequelae, and mortality.

After collection, data were analyzed using descriptive statistics. Variables were expressed in absolute and relative frequencies and subsequently compared with the literature.

The study was approved by the Research Ethics Committee of Hospital do Servidor Público Estadual (protocol number 25595419.9.0000.5463) on June 03, 2020, under consolidated opinion number 4.067.426. Because the study used retrospective data from medical records and preserved patient anonymity, informed consent was waived.

Results

Initially, a total of 57 patients with suspected DRESS were identified. After the RegiSCAR score was applied, and based on clinical and laboratory data from medical records, 5 patients were classified as negative and were excluded from the study. The remaining 52 patients were included, of whom 19 were classified as possible, 19 as probable, and 14 as definitive cases.

Patient age ranged from 5 to 89 years, with a mean age of 54.9 and a median age of 61 years. DRESS mostly affected those aged > 45 years and older patients (Figure 1). Twenty-seven (52%) patients were women and 25 (48%) were men. Forty-two patients had one or more associated comorbidities – the most common was cardiovascular disease (44,2%), followed by endocrinopathies (38.4%), current neoplasms (21.1%), nephropathies (13.4%), atopy (7.6%), rheumatologic disease (5.7%), mental disorders (5.7%), epilepsy (3.8 %), and chronic bowel disease (1.9%) (Table 2).

Fifty-one patients had laboratory tests described in their medical records, which included the following alterations: eosinophilia in 74.5%, atypical lymphocytes in 19.6%, liver dysfunction in 66.7%, and renal dysfunction in 36.7%. In systemic involvement assessment, of 52 patients, 36 (69.23%) had fever. Of the analyzed patients, 72.4% had low immunoglobulin levels during the DRESS episode (Table 3). Thirty-nine patients had skin manifestations – maculopapular rash was the most common (74.4%), followed by erythroderma desquamativum in 12.8%, bullous pemphigoid in 5.1%, pustular rash in 5.1%, and erythematous-violaceous patches in 2.6% (Figure 2).

The suspected cause of DRESS was a drug class in 40 patients. Anticonvulsants were the most prevalent (17), followed by antibiotics (15), nonsteroidal anti-inflammatory drugs (4), xanthine oxidase inhibitors (2), antiretrovirals (1), and minocycline (1). Analysis of isolated and concomitant drug therapy showed that antibiotics was the most prevalent class, and the most common group among them was beta-lactams (Table 4). Mean time of medication use prior to DRESS onset was 2.1 weeks. In addition to withdrawing the suspected medication, all patients were treated with corticosteroids. Only 3 patients received intravenous immunoglobulin combined with corticosteroid treatment.

Of the analyzed patients who died, the cause of death was acute DRESS in 4 (7%) and secondary causes in 8 (14%) (Figure 3). All patients who died had one or more comorbidities associated with DRESS.

At clinical follow-up, 12 patients were scheduled to perform a patch test to identify the offending medication, but only 3 (5.7%) attended the appointment. The suspected medication was confirmed in two patients

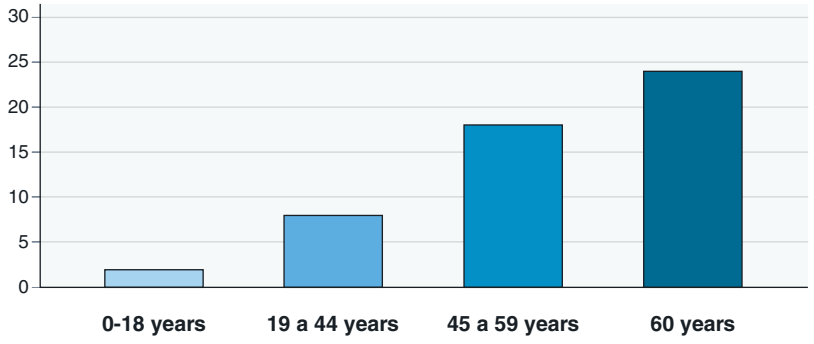

Figure 1
Patient distribution by age group

Table 2
Analysis of patient comorbidities

Comorbidities		N	%
Cardiovascular disease	SH	18	34.6%
	Arrhythmia	1	1.9%
	SH + arrhythmia	2	3.8%
	SH + heart failure	1	1.9%
	SH + dyslipidemia	1	1.9%
Endocrinopathies	Diabetes	11	21.1%
	Hypothyroidism	3	5.7%
	Diabetes + hypothyroidism	6	11.5%
Neoplasms	Brain neoplasms	8	15.3%
	Other neoplasms	3	5.7%
Nephropathies		7	13.4%
Atopy		4	7.6%
Rheumatologic disease		3	5.7%
Mental disorders		3	5.7%
Epilepsy		2	3.8%
Chronic bowel disease		1	1.9%

SH = systemic hypertension.

(1 positive for carbamazepine and 1 for amoxicillin), whereas the third patient tested negative for the suspected medication.

Discussion

In this study, 36.5% of patients were classified as possible cases, 36.5% as probable cases, and 27% as definitive cases. Cacoub et al. identified 20% of possible cases, 45% of probable, and 27% of definitive, whereas Kardaun et al. found 56 possible cases, 59 probable cases, and 59 definitive cases. This variation may be explained by the diagnosis being dependent on medical knowledge. Most doctors are not familiar with DRESS, which may hinder early notification and laboratory testing, as some test

Table 3
Laboratory test alterations in patients

Laboratory findings	%
Atypical lymphocytes	19.6%
Eosinophilia	74.5%
Altered liver function	66.7 %
Altered kidney function	36.7%
Reduced immunoglobulin (Ig) levels	Total: 72.4%
	IgM: 51.7%
	IgG: 24.1%
	IgA: 17.2%

Table 4
Medications associated with DRESS

Drug class	Medication	N
Anticonvulsants (17)	Phenytoin	6
	Carbamazepine	6
	Phenobarbital	2
	Others	5
Antibiotics (15)	Beta-lactams	18
	Sulfonamide	3
	Others	5
NSAIDs (4)	Dipyrone	11
	Others	4
Xanthine oxidase inhibitors		2
Other isolated medication		2
Antibiotics + NSAIDs		9
Other concomitant drugs (2 or more)		3

NSAID = nonsteroidal anti-inflammatory drugs.
DRESS = drug reaction with eosinophilia and systemic symptoms.

alterations are only relevant during the first days of onset. Furthermore, the recognition of the condition and complete collection of clinical and laboratory data are often complex, which can lead to confusion and delay the diagnosis.[1,4]

Patient age ranged from 5 to 89 years, with a mean age of 54.98 years, and 52% were women. According to Cabaña et al., DRESS can also occur in children, but mostly affects adults and has no gender predilection.[9] However, Kaurdaun et al. found a predominance of the female sex, as well as Perelló et al., who observed a higher rate of adverse drug reactions in women. This may be explained by the fact that women seek health services more often and take more medication than men.[4,10]

In the study by Kardaun et al., most patients had seizure disorders (20%), followed by diabetes (12%), cardiovascular disease (8.5%), previous kidney disease (6%), liver disease (5.1%), and recent cancer (5.1%). In our study, the most common comorbidity was cardiovascular disease (44.2%),[4] but endocrinopathies were also coincidentally the second most common. We found a higher prevalence of associated comorbidities than other studies, which could be explained by the greater number of adults and older adults included in the sample. These age groups tend to present more comorbidities, especially diseases of the cardiovascular system.[11] Oliveira and Moraes Jr. explain that the greater the number of comorbidities, the greater the number of medications being used and, consequently, the greater the chances of DRESS.[12]

When evaluating systemic involvement, 69.2% of patients had fever, which is considered one of the most common signs of DRESS.[8] In the study by Kardaun et al., 90% of patients with DRESS had fever.[4]

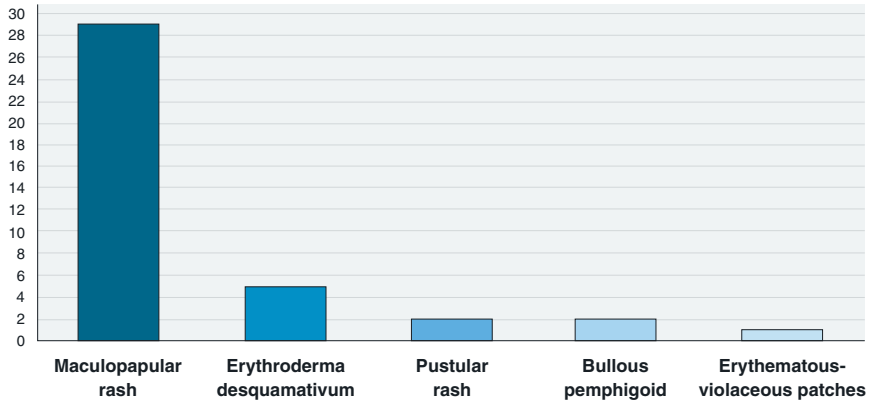

Figure 2
Distribution of skin lesions

Regarding laboratory alterations, 19.6% of patients had atypical lymphocytes, 74.5% had eosinophilia, 66.7% had altered liver function, and 36.7% had altered renal function. Of analyzed patients, 72.4% had decreased immunoglobulin levels during the DRESS episode. These values are similar to those reported by Cho et al.: eosinophilia in 66%-95% of cases, atypical lymphocytes in 27%-67%, liver alterations in 75%-94%, and renal alterations in 12%-40%. They also reported that some studies have demonstrated the presence of transient hypogammaglobulinemia during the initial stages of DRESS due to a decrease in B lymphocytes during this period.[5]

Watanabe and Gouveia et al. reported that the lesion most commonly associated with DRESS is maculopapular rash, which is in accordance with the 74.4% rate of maculopapular rash found in this study.[8,13]

Anticonvulsants, when used alone, were the most common class of drugs implicated in DRESS in this study, as well as in the studies by Kardaun et al.[4] and Cacoub et al.[1] In these same studies, the most prevalent anticonvulsant was carbamazepine, which was also one of the most prevalent in our study, as well as phenytoin. Ang et al. reported a high prevalence of phenytoin among offending medications.[14] Perello et al. also found anticonvulsants to be the main offending

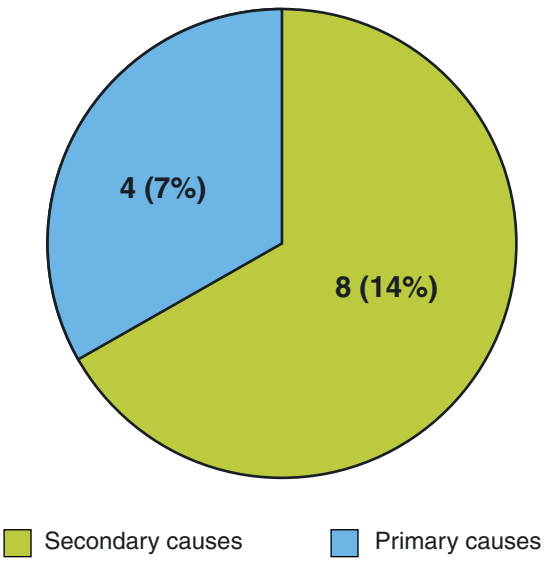

Figure 3
Patients who died due to primary or secondary causes

drug class when assessing serious adverse drug reactions, followed by beta-lactam antibiotics.[10]

Antibiotics were the second most common drug class. Kardaun et al. found a 25% prevalence of antibiotics (12% sulfonamide and 13% other antibiotics), with sulfonamide being the most common, but in our study the most prevalent class was beta-lactams.[4] A possible cause for the higher prevalence of beta-lactams is the fact that these are the most commonly used class of antibiotics today.[15] Cacoub et al. observed delayed symptom onset, typically 2 to 6 weeks after using the medication.[1] Kano et al. also reported that DRESS symptoms typically appear 2 weeks after starting the medication.[16] In this study, we found a mean time of medication use prior to DRESS onset of 2.1 weeks. Regarding treatment, all patients received systemic corticosteroids at an initial dose of approximately 1 mg/kg/day, and only 3 patients received immunoglobulin in association with corticosteroids. According to Ferreira et al., first-line treatment (concomitantly with withdrawn of the medication) consists of systemic corticosteroids at a dose of 0.5 to 1 mg/kg/day, with gradual dose reduction, and immunoglobulin, which should not be used as monotherapy in cases of DRESS. However, the use of immunoglobulin is controversial because of possible adverse effects.[1,3]

We found a DRESS mortality rate of 7%, similar to the rate of 2%-14% found by Watanabe.[8] Cacoub et al. also found a mortality rate of approximately 10%.[1]

Conclusion

In this study, DRESS most commonly affected women, adults, and older adults, and the most common comorbidity was cardiovascular disease. Fever was the most prevalent clinical manifestation, and eosinophilia was the most frequent laboratory alteration.

The predominant cutaneous manifestation was maculopapular rash, and anticonvulsants, when used alone, were the main class of drugs implicated in DRESS. Mean time of medication use prior to DRESS onset was 2.1 weeks, and all patients received systemic corticosteroids as the main treatment. Only 3 patients received human immunoglobulin as an additional treatment.

In conclusion, DRESS is a severe and potentially fatal complex syndrome whose diagnosis is challenging. The RegiSCAR score was shown to be an important aid in confirming the diagnosis and differentiating it from other diseases. The mortality rate highlights the severity of the condition. Identifying and withdrawing the offending medication, as well as starting treatment early, has a key role in patient recovery.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Dina Larissa Capelasso da Costa
E-mail: larissacapelasso@gmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Oral food challenge: a Brazilian panorama

Teste de provocação oral com alimentos: o panorama brasileiro

Lucila Camargo Lopes de Oliveira[1,2], Jackeline Motta Franco[3,4], Ana Carolina Rozalem Reali[1], Ana Paula Beltran Moschione Castro[1,5], Ariana Campos Yang[1,6,7], Bárbara Luiza de Britto Cançado[1], Fabiane Pomiecinski Frota[1], Germana Pimentel Stefani[1], Ingrid Pimentel Cunha Magalhães Souza Lima[1], José Carlison Santos de-Oliveira[1], José Luiz Magalhães Rios[1], Nathalia Barroso Acatauassú Ferreira[1], Renata Rodrigues-Cocco[1,8], Valéria Botan-Gonçalves[1], Norma de Paula M. Rubini[9], Emanuel Sarinho[10], Dirceu Solé[2,11]

ABSTRACT

Background: Oral food challenge (OFC), the gold standard for diagnosing food allergy and determining tolerance levels, requires specialized staff and appropriate conditions since anaphylaxis may occur. In 2022, OFC was officially recognized in Brazilian public and private health systems, although only for milk allergy in children up to 24 months of age. Little is known about OFC practices in Brazil. **Objectives:** To explore OFC practices, barriers, and solutions among Brazilian allergists and immunologists. **Methods:** A survey was e-mailed to 2500 associates of the Brazilian Association of Allergy and Immunology regarding OFC practices, training experiences, barriers to this procedure, and workable solutions. **Results:** A total of 290 associates responded (11.6%), more than a half of whom (56.15) practiced in the southeast region: 158 (54.5%) reported performing OFC, of whom 62% performed > 5 procedures each month, mostly for cow milk and hen egg. OFCs were mostly performed in private practice and were associated with specialized training. Lack of an appropriate setting was seen as the main barrier to performing the procedure.

RESUMO

Introdução: O teste de provocação oral (TPO) com alimentos é o padrão ouro para avaliação diagnóstica e de aquisição de tolerância em pacientes com alergia alimentar (AA). Exige, no entanto, equipe especializada e local apropriado para execução, uma vez que reações alérgicas, incluindo anafilaxia, podem acontecer. Foi recém-incorporado como procedimento reconhecido pelo Sistema Único de Saúde e pela Agência Nacional de Saúde, mas apenas no contexto da alergia ao leite de vaca para pacientes com até 24 meses de vida. Pouco se sabe sobre sua disponibilidade/execução no território brasileiro. **Objetivos:** Explorar o perfil de realização de TPO com alimentos em âmbito nacional, bem como as limitações para a sua não realização. **Métodos:** Inquérito virtual foi disponibilizado por e-mail aos 2.500 sócios cadastrados na Associação Brasileira de Alergia e Imunologia questionando sobre a prática de TPO, formação do profissional, limitações para sua não realização e possíveis soluções para sua execução. **Resultados:** Foram obtidas 290 respostas (11,6% dos associados), sendo a maioria deles proveniente da Região Sudeste (56,1%). Realizam

1. ASBAI (2021-2022), Scientific Department of Food Allergy - São Paulo, SP, Brazil.
2. Universidade Federal de São Paulo (USP), Escola Paulista de Medicina (UNIFESP-EPM), Allergy and Clinical Immunology, Department of Pediatrics - São Paulo, SP, Brazil.
3. ASBAI (2021-2022), Coordinator of the Scientific Department of Food Allergy - Aracajú, SE, Brazil.
4. Universidade Federal de Sergipe, Food Allergy Service - Aracajú, SE, Brazil.
5. School of Medicine, USP, Allergy and Immunology Unit, Instituto da Criança e Adolescente, Hospital das Clínicas - São Paulo, SP, Brazil.
6. School of Medicine, USP, Allergy and Clinical Immunology Service, Hospital das Clínicas - São Paulo, SP, Brazil.
7. School of Medical Sciences, UNICAMP, Allergy and Immunology - Campinas, SP, Brazil.
8. Faculdade Israelita de Ciências da Saúde Albert Einstein - São Paulo, SP, Brazil.
9. ASBAI (2021-2022), Scientific Director - Rio de Janeiro, RJ, Brazil.
10. ASBAI (2021-2022), Chair - Recife, PE, Brazil.
11. ASBAI (2021-2022), Research Director - São Paulo, SP, Brazil.

Submitted April 06 2023, accepted April 14 2023.

Arq Asma Alerg Imunol. 2023;7(2):171-80.

http://dx.doi.org/10.5935/2526-5393.20230023-en

Conclusions: Although this study's methodology involves intrinsic biases, this is the first exploration of OFC practice in Brazil. OFCs are still underperformed nationwide.

Keywords: Food hypersensitivity, diagnosis, prognosis, food.

TPO 54,5% (158/290) dos associados, 62% destes mais de 5 TPOs/mês, principalmente para leite e ovo. A execução de TPO na atualidade, majoritariamente na rede privada, esteve associada à prática do procedimento durante a especialização. Falta de recurso e ambiente apropriados são as maiores limitações para a não realização do TPO. **Conclusões:** Apesar do viés de seleção inerente à metodologia empregada do estudo, este inquérito pioneiro em território nacional tem importância por esclarecer e discutir a realização do TPO no âmbito do Brasil. Certamente este procedimento ainda é insuficientemente realizado no Brasil.

Descritores: Hipersensibilidade alimentar, diagnóstico, prognóstico, alimentos.

Introduction

The worldwide prevalence of food allergy (FA) is estimated to range from 1% to 10%, affecting people of different ages, ethnicities, and socioeconomic conditions.[1] Approximately 30% of children with FA may experience reactions to multiple food allergens.[2] Data on the prevalence of FA in the Brazilian population are scarce. A national multicenter study observed high sensitization rates, mainly to cow's milk (84.2%) and egg (70.5%), in a selected population with a medical diagnosis of FA. [3] It also showed a significant increase in sensitization to cow's milk, peanuts, and corn from 2004 to 2016.[3,4]

The symptoms of FA are nonspecific, and laboratory tests alone are not sufficient to confirm or exclude the diagnosis. The oral food challenge (OFC) is still considered the diagnostic gold standard for FA when performed in a double-blind, placebo-controlled manner.[5] The OFC is also used to investigate acquisition of tolerance to food allergens, which can happen spontaneously or be induced (immunotherapy).[5] However, it needs to be performed in a specialized setting by a trained professional, as it poses a risk of anaphylaxis, a potentially fatal allergic reaction.[6-8] Elimination diet remains the cornerstone of FA management, which may imply nutritional risk, especially for patients with allergies to multiple food allergens.[9] Therefore, a thorough investigation is essential to avoid misdiagnosis and thereby prevent the implementation of unnecessary diets, which reduce quality of life.[10] The OFC is associated with better QoL independent of challenge outcome because it elucidates some aspects of the FA.[11]

Of note, the OFC has only been covered by the Brazilian Unified Health System (Sistema Único de Saúde, SUS) and private health insurances (Brazilian Hierarchic Code of Medical Procedures/TUSS code 2.01.01.36-8) since 2022, and only for children aged up to 24 months in need of diagnosis and/or monitoring of allergy to cow's milk.[12,13]

Considering the increase in the prevalence of FA in recent decades, as well as the incipient inclusion of the OFC in private and public health systems and its complexity, it is likely that the test is insufficiently performed in Brazil. With the objective of describing the profile of OFC performance in Brazil, including barriers, the Scientific Department of Food Allergy of the Brazilian Association of Allergy and Immunology 2021-2022 (ASBAI) conducted a survey on the topic to be answered by ASBAI members.

Methods

This was a cross-sectional study that assessed OFC performance by allergists and immunologists. Participants answered an on-line questionnaire on Google Forms® (Annex 1).

All 2,500 ASBAI members received an institutional e-mail between June and December 2022 inviting them to participate in the survey, with a link to the questionnaire and the informed consent form. The 15 members of ASBAI's Scientific Department of Food Allergy were excluded from the survey to avoid bias.

The study was approved by the research ethics committee of Universidade Federal de São Paulo under no. 5.421.086 (0241/2022).

Categorical variables were expressed as frequencies and proportions and compared using Fisher's exact test. Statistical analyses were performed using Epi Info 7.2.5.0.

Results

One of the respondents did not provide informed consent and was excluded from the study. A total of 290 respondents (11.6%) were included, of whom 96.9% had completed medical residency or a fellowship program in Allergy and Immunology, and 45.5% of them had finished their residency/fellowship at least 10 years ago. Education-related characteristics, such as time since residency/fellowship completion and OFC training during residency/fellowship, are presented in Table 1 in relation to whether or not OFC is offered in clinical practice. In our sample, 106 physicians (36.5%) did not perform OFC during residency/fellowship, of whom 40 (37.7%) had completed their education in the last 19 years.

Not offering OFC in clinical practice was statistically higher in the group of physicians who completed their residency/fellowship between 20 and 29 years ago. Those who performed OFC during their medical education were more likely to offer OFC in current clinical practice ($p < 0.01$), especially if 6 or more OFCs were performed (Table 1).

Figure 1 shows the distribution of respondents according to the state where they work. Three physicians reported working in more than 1 state. Most respondents (n = 158 [54.5%]) reported offering OFC in current clinical practice, especially in the private sector (Figure 2). Just over 62% of these professionals perform up to five OFC with food monthly, and almost 16% perform 11 or more tests/month.

Table 1
Education-related characteristics of physicians who offer vs do not offer OFC (presented in absolute numbers and percentages)

	Offers OFC n = 158	Does not offer OFC n = 132	p*
No. of physicians who specialized in Allergy/Immunology (%)	154 (97.4%)	127 (96.2%)	1.00
Time since residency/fellowship completion			
Between 1 and 5 years ago	42 (27.3%)	23 (18.0%)	0.09
Between 6 and 10 years ago	39 (25.3%)	24 (18.9%)	0.25
Between 11 and 19 years ago	37 (24.0%)	27 (21.3%)	0.69
Between 20 and 29 years ago	21 (13.7%)	35 (27.6%)	< 0.01
30 years ago or more	15 (9.7%)	18 (14.2%)	0.27
Number of OFCs performed during residency/fellowship			
0	40 (26%)	66 (52%)	< 0.01
Up to 5	24 (15.6%)	29 (22.8%)	0.13
Between 6 and 10	17 (11.0%)	5 (3.9%)	0.04
More than 10	73 (47.4%)	27 (21.3%)	< 0.01

OFC = oral food challenge.

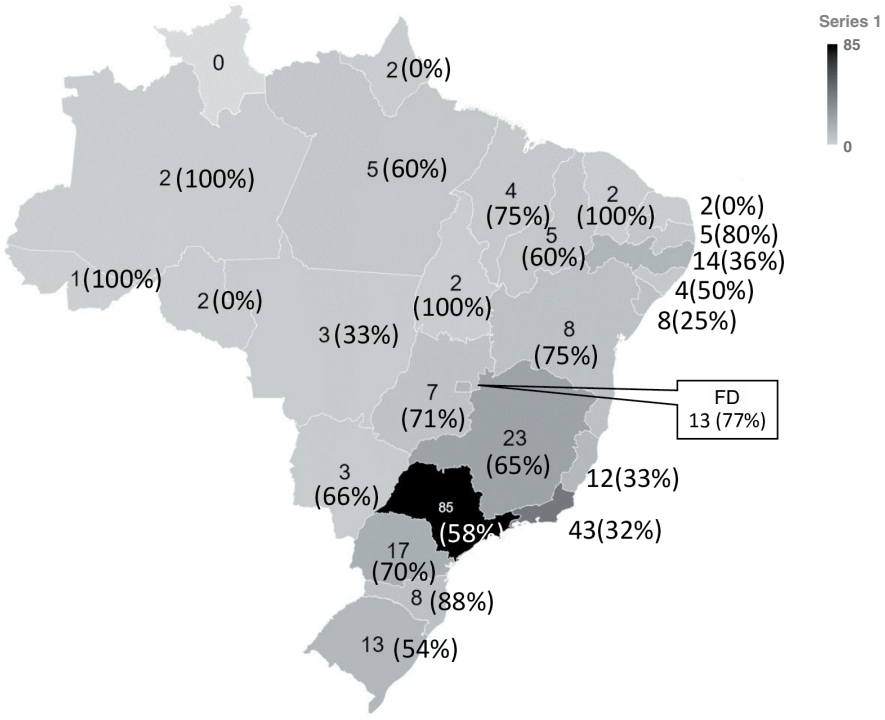

Figure 1
Distribution of physicians according to state (n = 293). In parentheses = percentage of physicians who offer the oral food challenge
FD = Federal District.

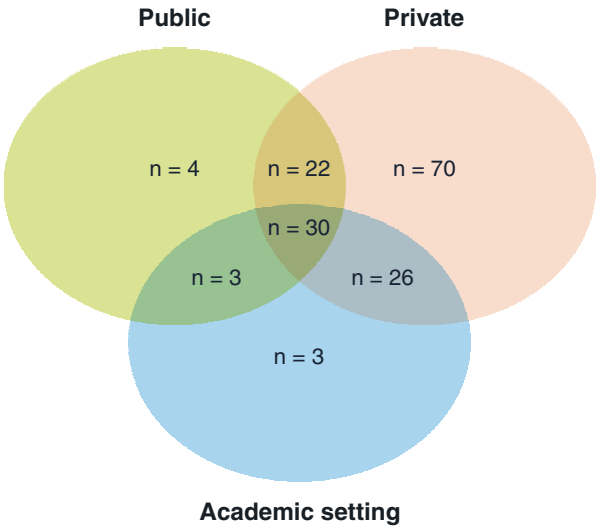

Figure 2
Distribution of physicians (n = 158) who offer the oral food challenge according to each sector

As for the environment in which OFC is commonly performed, most respondents (38%) answered the hospital environment, followed by out-of-hospital/outpatient (28.5%), both (25.3%), and the rest, level III centers. Most physicians obtain informed consent from patients/guardians (89.9%). Cow's milk (83.5%) and egg (11.4%) are the most tested foods, followed by seafood (3.2%).

Figure 3 shows the types of OFC most commonly performed (open, single-blind, or double-blind and placebo-controlled). The single-blind method is the most performed, and 74% of respondents reported only performing this method. The food is most often provided by the family (67.1%), followed by the doctor (20.3%) and nutritionist/medical staff member (12%). The food is more commonly administered to the patient by the doctor (82.3%) or a nurse/practical nurse (13.3%), and a nutritionist is only involved in 1.9% of cases.

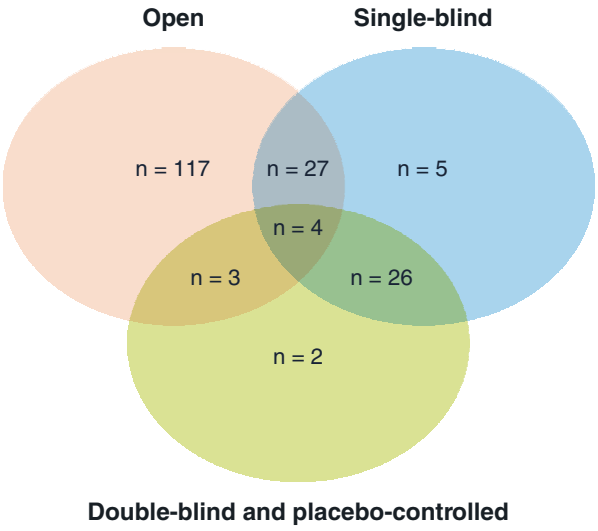

Figure 3
Number of physicians who perform each type of oral food challenge (n = 158)

A hundred and fifty-two physicians (45.5%) reported not offering OFC due to the following barriers: lack of appropriate resources and space (46%), lack of technical capacity (21%), inadequate reimbursement (12%), lack of health insurance (11%), and patient or family refusal (2%). Among suggested solutions (1 possible answer in the multiple-choice test), the availability of standardized national protocols for performing OFC was selected as the best one (Figure 4).

Discussion

Brazil is estimated to have a rate of 0.94 allergists/immunologists per 100,000 inhabitants under the age of 18 – more than Canada (0.67) and Australia (0.87) but much less than Germany (6.50) and Japan (3.34).

Data from this survey were obtained from all Brazilian states, except Roraima (Figure 1). The questionnaire was answered only by a small number of ASBAI members (11.6%) who voluntarily agreed

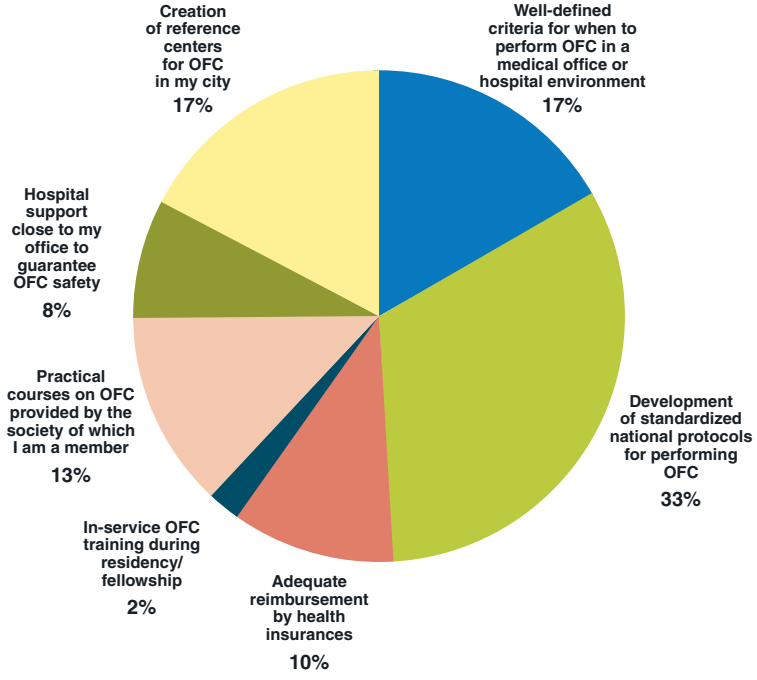

Figure 4
Solutions suggested by physicians (n = 123) who do not offer the oral food challenge (OFC)

to participate in the survey. Most respondents (n = 158/290, 54%,) reported offering OFC.

The rate of respondents was low but close to that observed in a similar US survey (10%).[15] However, 95% of respondents in the US survey reported offering OFC.[15] A similar survey conducted in Canada obtained a response rate of 30.2%, and 80.6% of respondents reported offering OFC.[16] In our Brazilian survey, a little over half of respondents reported offering the test, although most of them work in teaching hospitals (n = 62/158, 39%). This suggests that, despite a selection bias in favor of offering the test, OFC training is not a part of medical education in many teaching hospitals, meaning that misdiagnosis may be common. Of note, it is likely that those who do not offer this type of intervention tend to not participate in this type of survey.

Specialists who completed their residency/fellowship between 20 and 29 years ago offer less OFC in current clinical practice, probably because during their education the prevalence of FA was lower and medical residency programs did not provide OFC training. Although the rate of FA has significantly increased worldwide in the last 30 years and in Brazil in the past 2 decades, we still cannot quantify the real problem at the national level due to the scarcity of prevalence studies. No statistically significant difference was observed in those who completed their residency/fellowship > 30 years ago, probably due to the small number of respondents that constituted this group.

The performance of ≥ 5 OFCs during medical education was associated with OFC performance in current practice, showing the importance of including the procedure in medical education. More than a third (106/290) of respondents said they did not perform OFC during their residency/fellowship, higher than the rate of 29% observed in the US survey.[15]

Almost all of the allergists/immunologists who perform OFC work in more than one sector, including the private sector (148/158), and very few work exclusively in SUS (4/158) (Figure 2), meaning that most of the Brazilian population is likely to not have access to this test. Most physicians who offer OFC live in the Federal District and the Southeast Region of Brazil, possibly as a result of higher medical density in these regions, or selection bias.[17] It was recently estimated that 63.1% of ASBAI's members live in the Southeast Region of Brazil, followed by the Northeast (15.0%), South (9.7%), Midwest (7.7%), and North (4.4%) regions.[18]

A Canadian study reported a median of 12 OFCs per month per physician.[16] In our survey, 62% of physicians performed up to 5 OFCs per month, and 16% performed ≥ 11 OFCs per month.

The most tested foods are cow's milk and egg, followed by seafood, peanuts, and chestnuts. As in other countries, the open challenge is the most offered,[14,15] supposedly because it is less complex. It should be noted that the rate of Brazilian physicians who obtain informed consent was similar to that of US physicians (89.9% vs. 82%)[15] but higher than that of Canadians (40%).[16] Although the food to be tested is often provided by family members, the doctor is the one to administer it to the patient, similarly to what happens in the USA, where the food is administered by a nurse in 73% of cases.[15]

Unlike in the US and Canadian surveys, inadequate reimbursement was not mentioned among the main barriers[15,16,19] by those who do not offer the test, but rather lack of appropriate resources and space (46%) and lack of technical capacity (21%). However, in Canada, dedicated reimbursement fee codes were suggested by 66.1% of respondents.[16] Lack of support staff and office space was identified as a limitation by 72.6% and 64.5% of Canadian respondents, respectively.[16]

Conclusion

Only a little over 50% of respondents reported offering OFC in the setting of FA, which is concerning, as the absence of testing may lead to misdiagnosis and generate unnecessary diet restrictions with nutritional risks for patients. Furthermore, we suggest that OFC should be included in medical education and complemented by refresher courses.

After the incorporation of OFC in the SUS and private health insurances, together with the increase in FA prevalence in Brazil, we expect that the demand for OFC will increase similarly to that observed in other studies. Only a little over half of the allergists/immunologists who participated in this survey claimed to offer OFC. However, we cannot rule out selection bias, as it is likely that those who do not perform OFC have chosen not to participate in this survey, which means that the frequency of OFC may be overestimated.

This study showed that access to this important diagnostic tool is very limited in Brazil, which is concerning for a country of continental dimensions.

The technical training of more professionals, either by including OFC training in residency/fellowship programs or by promoting refresher courses, is necessary. The lack of appropriate resources and spaces is also a concern that hinders the implementation and dissemination of the OFC.

Despite the selection bias inherent to the methodology used in this study, this pioneering Brazilian survey is important to understand and discuss the performance of this type of procedure in Brazil.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Lucila Camargo-Lopes-de-Oliveira
E-mail: lucila_camargo@yahoo.com

Annex 1

On-line questionnaire on performing oral food challenge (OFC) aimed at specialists in allergy/immunology

Oral food challenge: Brazilian panorama

The oral food challenge (OFC) is still considered the diagnostic gold standard for food allergies (FAs) and is also used to investigate the acquisition of tolerance in patients with a previous diagnosis of FA. However, the test is not easy to perform, and it is different from food reintroduction at home. We developed this short questionnaire (approximate duration: 7 minutes) to better understand the barriers to OFC performance by ASBAI members, and we count on your valuable contribution!

ASBAI'S Scientific Department of Food Allergy (2021-2022)

Education

Did you undergo residency/fellowship training in Allergy and Immunology?

o Yes
o No

How long ago did you complete your residency/fellowship training in Allergy and Immunology?

o Between 1 and 5 years
o Between 6 and 10 years
o Between 11 and 19 years
o Between 20 and 29 years
o 30 years ago or more
o I did not undergo residency/fellowship training in Allergy and Immunology

How many OFCs did you perform during the entire period of your residency/fellowship program?

o Up to 5
o Between 6 and 10
o More than 10

In which Brazilian state (or the Federal District) do you currently work? You may select more than one option.

o Acre
o Alagoas
o Amapá
o Amazonas
o Bahia
o Ceará
o Federal District
o Espírito Santo
o Goiás
o Maranhão
o Mato Grosso
o Mato Grosso do Sul
o Minas Gerais
o Pará
o Paraíba
o Paraná
o Pernambuco
o Piauí
o Rio de Janeiro
o Rio Grande do Norte
o Rio Grande do Sul
o Rondônia
o Roraima
o Santa Catarina
o São Paulo
o Sergipe
o Tocantins

Annex 1 *(continuation)*
On-line questionnaire on performing oral food challenge (OFC) aimed at specialists in allergy/immunology

Have you taken any of the following courses? You may select more than one option.
o Advanced Life Support in Anaphylaxis and Asthma (ALSAA)
o Advanced Cardiovascular Life Support (ACLS)
o Pediatric Advanced Life Support (PALS)
o None of the above

Do you offer OFC in your clinical practice?
o Yes
o No

For those who offer OFC in clinical practice

In which sector do you work as an allergist/immunologist? You may select more than one option.
o Public
o Private
o Teaching hospital (both private and public)

What age group do you treat?
o Children and adolescents
o Adults and older adults
o All age groups

In the last 12 months, how many patients with suspected FA did you treat on average?
o Up to 5 patients
o Between 6 and 10 patients
o Eleven patients or more

In the last 12 months, how many OFCs did you perform per month on average?
o Up to 5
o Between 6 and 10
o Eleven or more

In what percentage of patients with suspected FA do you perform OFC?
o Up to 25%
o 25% to 50%
o More than 50%

When choosing the appropriate environment for performing OFC, you take into consideration:
o The mechanism involved in the reaction (IgE-mediated or non-IgE-mediated)
o Severity of reaction
o Both

In which environment do you typically perform OFC?
o Hospital environment
o Out-of-hospital/outpatient environment
o Both

Do you recommend food reintroduction at home for patients with a diagnosis of non-IgE-mediated FA and for those with a history of immediate reaction without sensitization?
o Yes
o No

If yes, has a patient ever had a severe reaction during reintroduction at home?
o Yes
o No
o I do not recommend food reintroduction at home for non-IgE-mediated cases nor for those with a history of immediate reaction without sensitization

Annex 1 *(continuation)*

On-line questionnaire on performing oral food challenge (OFC) aimed at specialists in allergy/immunology

Do you obtain informed consent from patients/guardians?
o Yes
o No

Which food is more commonly tested in your clinical practice?
o Cow's milk
o Egg
o Soy
o Wheat
o Fish
o Seafood
o Peanuts and chestnuts
o Other

What type of OFC do you offer in your clinical practice? You may select more than one option.
o Open (patient, family, and doctor know which food is being administered)
o Single-blind (2-stage procedure with the food and a placebo; only the doctor knows which food is being administered)
o Double-blind and placebo-controlled (2-stage procedure with the food and a placebo, but not even the doctor knows which food is being administered)

Who provides the food that will be administered to the patient?
o Patient's family
o You (doctor)
o Nutritionist or a medical staff member
o Other

Who typically administers the food to the patient?
o You (doctor)
o Nutritionist
o Nurse/practical nurse
o Other

For those who do NOT offer OFC

What would you describe as the main barrier to performing OFC?
o Risk of adverse effects
o Lack of technical capacity
o Lack of appropriate resources and space
o Patient or family refusal
o Inadequate reimbursement
o Lack of private health insurance

Among the options below, what would you say is the best solution to overcome these barriers?
o Well-defined criteria for when to perform OFC in a medical office or hospital environment
o Standardized national protocols for performing OFC
o Adequate reimbursement by health insurances
o In-service OFC training during residency/fellowship training
o Periodic practical courses on OFC provided by the society of which I am a member
o Hospital support close to my office to guarantee OFC safety
o Creation of reference centers for OFC in my city

Please feel free to write further considerations on the topic below.

_____

_____

_____

Thank you for your valuable contribution!

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Allergic rhinitis among medical students: perceptions about diagnosis, symptom control, and quality of life

Rinite alérgica em estudantes de Medicina: percepção sobre diagnóstico, controle dos sintomas e qualidade de vida

Phelipe dos Santos Souza[1], Henrique de Rocco Echeverria[1], Ana Alice Broering Eller[1], Gabriel de Araujo Granado[1]

ABSTRACT

Introduction: Allergic rhinitis is a disease involving nasal symptoms, such as rhinorrhea, sneezing and nasal congestion, which are caused by mucosal inflammation due to allergen exposure. The symptoms, which affect patient quality of life, frequently include sleep problems, irritability, and fatigue. The disease can have a negative impact on academic performance in affected students. **Objective:** In view of the disease's effects on academic performance, this study determined the prevalence of allergic rhinitis among medical students at the Universidade do Vale do Itajaí (Santa Catarina, Brazil), identifying the degree to which it impairs quality of life and relating this to symptom control. **Methods:** This descriptive observational study was based on data collected from medical students through 2 specific questionnaires to assess symptom control and quality of life: the Rhinitis Control Assessment Test (RCAT) and Sino-Nasal Outcome Test (SNOT-22). **Results:** Among the 88 medical students evaluated in this study, the prevalence of allergic rhinitis was 69%. The disease controlled in most affected students, indicating a lower impact on quality of life. The most prominent symptoms were sneezing, nasal obstruction, and tearing. According to the RCAT and SNOT-22 results, symptom control was significantly correlated with quality of life ($r = -0.4277$; $p < 0.001$). **Conclusion:** Unlike the rest of the population, the students' knowledge of allergic rhinitis led to greater awareness of the condition and better treatment adherence. Therefore, educating the population is essential for symptom control and guaranteeing collective quality of life.

Keywords: Allergic rhinitis, medical students, quality of life.

RESUMO

Introdução: A rinite alérgica (RA) é uma doença com sintomas nasais, como rinorreia, espirros e congestão nasal, causada pela inflamação da mucosa após a exposição do indivíduo a um agente alérgeno. A sintomatologia da doença causa consequências na qualidade de vida do paciente, que frequentemente possui problemas de sono, irritabilidade e fadiga. Estudantes podem ter seu desempenho acadêmico afetado de modo negativo pela doença. **Objetivo:** Tendo em vista a problemática que a doença causa na performance de estudantes, esse estudo pretende analisar a prevalência da RA nos discentes da Universidade do Vale do Itajaí (UNIVALI), com a finalidade de identificar o grau de comprometimento na qualidade de vida dos estudantes com a doença e relacionar com o seu grau de controle dos sintomas da rinite alérgica. **Métodos:** Trata-se de um estudo descritivo observacional, a partir de dados coletados de estudantes de Medicina, através de questionários específicos para avaliação do controle dos sintomas e impacto na qualidade de vida, sendo eles: o *Rhinitis Control Assessment Test* e o *Sino-Nasal Outcome Test*. **Resultados:** 88 estudantes de Medicina foram avaliados neste estudo, a prevalência da RA foi de 69%. A maioria dos estudantes possui a doença controlada, o que caracteriza menor impacto da doença na qualidade de vida desses pacientes. Entre eles, os sintomas de maior impacto são: espirros, obstrução nasal e lacrimejamento ocular. Houve correlação estatística entre o controle dos sintomas e o impacto dos mesmos na qualidade de vida, avaliado pelos questionários RCAT e SNOT-22 ($r = -0,4277$; $p < 0,001$). **Conclusão:** O conhecimento disseminado entre estudantes de Medicina sobre rinite alérgica, diferentemente do resto da população, permite que os mesmos tenham maior conscientização, aderência aos tratamentos e percepção do quadro. Por isso, a educação da população se faz essencial e útil para controle dos sintomas e garantia da qualidade de vida coletiva.

Descritores: Rinite alérgica, estudantes de Medicina, qualidade de vida.

1. Universidade do Vale do Itajaí, Medical School - Itajaí, SC, Brazil.

Submitted Feb 19 2023, accepted Apr 18 2023.

Arq Asma Alerg Imunol. 2023;7(2):181-8.

http://dx.doi.org/10.5935/2526-5393.20230024-en

Introduction

Allergic rhinitis (AR) is a disease with nasal symptoms caused by exposure to specific allergens that induce an IgE-mediated inflammatory reaction.[1,2] This response is an immediate hypersensitivity reaction that produces IgE after exposure to an antigen, which binds to mast cell Fc receptors with subsequent release of its mediators.[3] Considered one of the most common chronic respiratory diseases, AR is a global health problem, affecting approximately 10% to 20% of the world's population.[1,4,5]

Symptoms of AR include clear rhinorrhea, nasal congestion, nasal itching, and sneezing. These symptoms are present for more than 1 hour on most days, for 2 or more consecutive days.[1] The onset of AR symptoms occurs most commonly in childhood, but the disease can begin at any age.[2]

The diagnosis of AR is essentially clinical, with a history of typical allergy symptoms.[1,5] The diagnosis is likely in patients with 2 or more of the typical symptoms of the disease for more than 1 hour on most days.[5]

AR treatment includes pharmacotherapy combined with environmental control and allergen avoidance. Pharmacologic options for the treatment of AR include antihistamines, decongestants, corticosteroids, leukotriene receptor antagonists, disodium cromoglycate, and immunotherapy.[6]

Health-related quality of life focuses on patients' perceptions of the impact of the disease on them.[7] AR symptoms have direct consequences for the patient's daily life. Fatigue, irritability, and sleep disturbances are commonly reported by patients with AR, affecting their productivity.[7,8]

Several instruments have been developed to assess the level of rhinitis control, including the Rhinitis Control Assessment Test (RCAT).[2,9] The RCAT was developed in English but translated into Portuguese and validated by Fernandes et al.[10] It consists of 6 questions that assess the intensity of symptoms over the past week, their interference with sleep and daily activities, and self-assessment of disease control. The final score ranges from 6 to 30, with scores of 21 or less indicating uncontrolled disease.[7]

In view of the close connection between disease control and patient quality of life, it is necessary to use a disease-specific questionnaire to effectively and reliably estimate the quality of life of each patient with AR, such as the 22-item Sino-Nasal Outcome Test (SNOT-22) designed to assess the impact of chronic rhinosinusitis (CRS) and nasal polyps on quality of life. As with any disease-specific questionnaire, it allows a better clinical assessment than general questionnaires. The SNOT-22 was translated into Portuguese and validated by Kosugi et al.[11] It was originally published in English as an adaptation of the SNOT-20, which in turn is derived from the 31-item Rhinosinusitis Outcome Measure (RSOM-31). The SNOT-22 has shown internal consistency, reproducibility, validity, and responsiveness nationwide, consisting of 22 items (symptoms) whose intensity is scored by patients from 0 (no problem) to 5 (problem as bad as it can be). In addition, it assesses whether the patient has undergone surgery for the problem in question (CRS or nasal polyps), scoring the degree of improvement after surgery.

Given that AR symptoms likely contribute to academic impairment in young people and students, the current study aimed to analyze the frequency of AR symptoms in university students, identify the impact of the disease on their quality of life, and relate it to their level of symptom control.

Methods

Participants

We conducted a cross-sectional observational study of students from the Universidade do Vale do Itajaí (UNIVALI) Medical School, southern Brazil. All medical students were invited to participate regardless of sex, ethnicity, or social status. All enrolled medical students who agreed to participate were included in the study. Students who did not agree with the previously established terms and those who did not answer certain questions that could compromise the results of the study were excluded.

Procedures

The study was approved by UNIVALI Research Ethics Committee (approval no. 4.885.968). Data were collected through virtual platforms via questionnaires containing questions covering patient age, sex, perceptions of the disease, and self-assessment of AR control. The participants also completed the RCAT and SNOT-22, both of which have been translated into Portuguese and validated for use in Brazil.

Instruments

RCAT assesses AR control and consists of 6 questions that refer to symptoms over the past week,

3 of which address nasal congestion, sneezing, and watery eyes. Two questions address the interference of symptoms with sleep and daily activities, and 1 question refers to self-perception of symptom control. Each question is scored from 1 to 5, where 5 = never, 4 = rarely, 3 = sometimes, 2 = often, and 1 = extremely often. The total score ranges from 6 to 30, with scores of 22 or more indicating controlled disease, and 21 or less indicating uncontrolled disease.

SNOT-22 was used to assess quality of life. This CRS- and nasal polyp-specific questionnaire consists of 22 items, each one corresponding to a specific symptom. Items are scored from 0 to 5 to assess the level of intensity of each symptom. Symptoms are scored as follows: 0 = no problem, 1 = very mild problem, 2 = mild or slight problem, 3 = moderate problem, 4 = severe problem, and 5 = problem as bad as it can be. The scores of each item are summed to form a total score of 0 to 110, with higher scores indicating greater impact of symptoms on quality of life.

Data analysis

The data obtained electronically were entered into Excel® spreadsheets and subsequently exported to BioEstat 5.0 and JASP version 0.14.1.0 for statistical analysis. Pearson's correlation coefficient was used to assess correlations between total quality of life scores and total AR symptom control scores. Results with a p-value <0.05 were considered statistically significant. The measures of central tendency used were mean and mode. Standard deviation (SD) was used as a measure of dispersion.

Results

The sample evaluated in the current study consisted of 88 medical students from a university in southern Brazil; 60 were women (68%), 27 were men, and 1 did not report sex. Mean participant age was 22 years, ranging from 17 to 33 years. The prevalence of AR was 69% (n = 61); of these, 68% (n = 42) were women.

Relationship between the sample and the questionnaires

In the 88 completed questionnaires, the mean RCAT score was 22 (SD, 4.4), noting that to be classified as controlled disease, a score of 22 or more should be obtained. The minimum score was 10, and the maximum score was 30 (Figure 1).

The mean SNOT-22 score was 37 (SD, 23.3), noting that this score ranges from 0 to 110, with higher scores indicating greater impact on patient quality of life. The minimum score was 0, and the maximum score was 100 (Figure 2).

There was no significant difference in mean RCAT scores between men and women. However, the mean SNOT-22 score was 34 for men and 38 for women. Participant age did not influence RCAT scores ($p = 0.3$), nor did it affect SNOT-22 scores ($p = 0.5$), since age ranged from 17 to 33 years.

Correlation between disease control and quality of life

The scatter plot in Figure 3 shows a negative correlation between symptom control and impact on quality of life ($r = -0.4277$; $p < 0.001$), that is, the more controlled the symptoms, the lower their impact on quality of life.

Analysis of symptom control in the sample

Among the 6 RCAT items, the one with the lowest mode value, that is, the least controlled category in the sample, was the frequency of sneezing, nasal congestion, and watery eyes (Table 1).

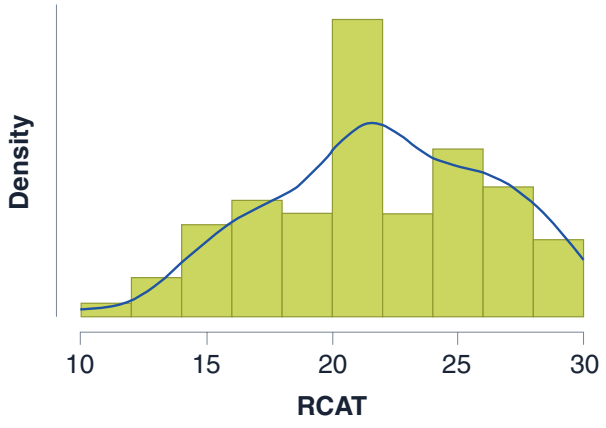

Figure 1
Sample distribution according to RCAT responses
RCAT = rhinitis control assessment test.

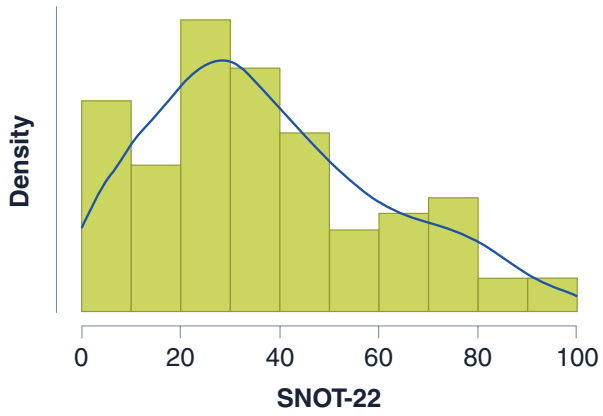

Figure 2
Sample distribution according to SNOT-22 responses
SNOT-22 = sino-nasal outcome test.

Analysis of the impact of symptoms on quality of life

To assess which symptom had the greatest impact on the students' quality of life, we used the mode values for the response to each symptom, as shown in Table 2. Among all SNOT-22 items, those with the highest mode value, that is, the ones that most interfered with quality of life, were "blockage/congestion of nose," "fatigue during the day," "sneezing," and "runny nose," all scored as a moderate problem (response 3).

Relationship between questionnaires and surgery

The most common surgical interventions were septoplasty (6%) and adenoidectomy (3%). The mean RCAT score was lower among the medical students who had already undergone surgery to improve CRS (mean score = 19.8). The mean SNOT-22 score was slightly higher in the students undergoing surgery than in those not undergoing surgery (mean score = 42.3). However, the difference in the mean scores between operated vs non-operated groups for both questionnaires was not statistically significant ($p > 0.05$). Table 3 shows the participants' perceptions after surgery.

Discussion

AR is characterized by an inflammatory reaction and the respective onset of typical allergy symptoms, often capable of interfering with patients' quality of life and daily activities.[12] In the current study, the

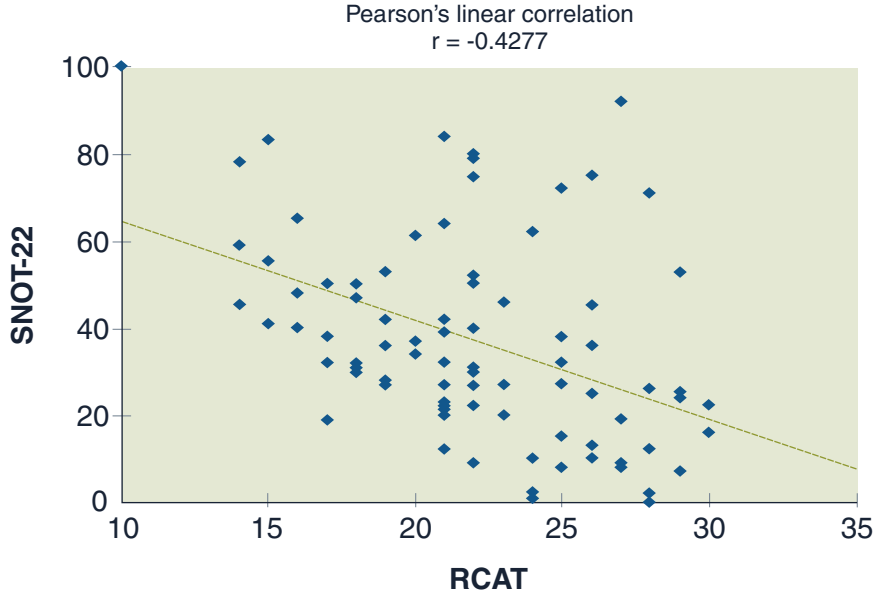

Figure 3
Correlation between symptom control (RCAT) and impact on quality of life (SNOT-22)
RCAT = rhinitis control assessment test; SNOT-22 = sino-nasal outcome test.

Table 1
RCAT questionnaire and participants' most frequent responses

Symptom	RCAT response (n; %)
During the past week, how often did you have nasal congestion?	3 (25; 28.4%)
During the past week, how often did you sneeze?	3 (27; 30.6%)
During the past week, how often did you have watery eyes?	4 (30; 34.0%)
During the past week, to what extent did your nasal or other allergy symptoms interfere with your sleep?	5 (40; 45.4%)
During the past week, how often did you avoid any activities (for example, visiting a house with a dog or cat) because of your nasal or other allergy symptoms?	5 (71; 80.6%)
During the past week, how well were your nasal or other allergy symptoms controlled?	3 and 4 (29; 32.9%)

RCAT = rhinitis control assessment test.

prevalence of AR in medical students was 69%, with female predominance, accounting for 68% of cases. The rate of AR in this sample was much higher than that of the Brazilian population, young people, and university students from other countries, with rates of 15%-25%.[9,13,14]

The higher prevalence found in our sample of medical students may be related to their knowledge of AR, thus leading to a greater perception of the condition and incidence of testing and diagnosis. Knowledge of the disease allows a more effective and appropriate treatment to be started promptly, with higher adherence rates, leading to greater symptom control and, consequently, better quality of life. For this reason, raising the awareness of the lay population is essential, given the difference in the impact of symptoms on quality of life when comparing the scores of our study sample with those of a sample of the general population, illustrated by the mean SNOT-22 score (37 vs 62, respectively),[11] noting that the most prevalent symptoms are the same in both samples, but less controlled in the general population.

The main AR symptoms include rhinorrhea, sneezing, and nasal congestion, which can begin at any age, but most commonly begin in childhood.[1,2] The current study is in line with the existing literature by showing that, among medical students, the most impactful symptoms also were nasal congestion, rhinorrhea, sneezing, and fatigue.[8,15]

The symptomatology and the respective quality of life impairment among the students are directly related to disease control, since the impact on quality of life decreases with increasing disease control. In this respect, our sample's mean score for the symptom control questionnaire (RCAT) was 22, while for the questionnaire on the impact of symptoms on quality of life (SNOT-22), it was 37. The mean score for these questionnaires in the general population was 20.4 (SD, 4.2) for the RCAT[16] and 62.3 (SD, 25.3) for the

SNOT-22,[11] suggesting that the study sample has greater control over the symptoms of the disease, and that the symptoms have a lower impact on the patients' quality of life.

Another point to be analyzed is surgical intervention in patients with AR. Overall, there was little improvement after surgical intervention, with a recurrence rate of about 30%, which may suggest persistent AR (14% of cases), and more complex interventions, such as vidian neurectomy, may be considered in cases of vasomotor rhinitis.[17]

AR is a disease with a significant prevalence that is probably underestimated, and therefore it is extremely important to raise the population's awareness of symptoms, which may lead to a higher rate of diagnosis and, consequently, better disease control. It is crucial to provide patients with effective guidance and education on environmental control measures, that is, avoiding exposure to allergens that trigger or aggravate symptoms.

It can be concluded that adequate control of AR symptoms favors a better quality of life in affected

Table 2
SNOT-22 questionnaire and participants' most frequent responses

Symptom	SNOT-22 response (n; %)
Need to blow nose	2 (26; 29.5%)
Sneezing	3 (24; 27.2%)
Runny nose	3 (21; 23.8%)
Cough	0 (40; 45.4%)
Post-nasal discharge (dripping at the back of your nose)	0 (30; 34.0%)
Thick nasal discharge	0 (39; 44.3%)
Ear fullness	0 (34; 38.6%)
Dizziness	0 (48; 54.5%)
Ear pain/pressure	0 (55; 62.5%)
Facial pain/pressure	0 (40; 45.4%)
Difficulty falling asleep	0 (33; 37.5%)
Waking up at night	0 (37; 42.0%)
Lack of a good night's sleep	0 (29; 32.9%)
Waking up tired	2 (23; 26.1%)
Fatigue during the day	3 (27; 30.6%)
Reduced productivity (in daily activities)	2 (21; 23.8%)
Reduced concentration (in daily activities)	2 (19; 21.5%)
Frustrated/restless/irritable	2 (21; 23.8%)
Sad	0 (29; 32.9%)
Embarrassed	0 (32; 36.3%)
Sense of taste/smell	0 (47; 53.4%)
Blockage/congestion of nose	3 (28; 31.8%)

SNOT-22 = sino-nasal outcome test.

Table 3
Relationship between surgical procedures and postoperative perceptions

After surgery, you felt:	Frequency	%	Surgery performed (n)
Slightly worse	1	7.6%	Adenoidectomy and tonsillectomy (1)
The same	3	23.0%	Septoplasty (3)
Slightly better	7	53.8%	Adenoidectomy (2), septoplasty (2), septoplasty and adenoidectomy (1), tonsillectomy (1), turbinectomy (1)
Much better	2	15.4%	Adenoidectomy (1), septoplasty (1)
Did not answer	0	0	
Total	13	100	

patients. In this respect, there was statistical significance between the responses in both questionnaires (RCAT and SNOT-22), which showed that factors such as sex and age did not interfere with symptom control or quality of life. In addition, symptom improvement was not related to surgical intervention, with a high rate of persistent AR among patients even after surgery. Therefore, the best option for the maintenance of AR remains effective guidance and education of the population.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Henrique de Rocco Echeverria
E-mail: henrique.echeverria@outlook.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Characteristics of patients with hypersensitivity reactions to chemotherapeutic and biological agents and desensitization behavior

Características de pacientes com reações de hipersensibilidade a agentes quimioterápicos e biológicos e comportamento de dessensibilização

Juan Camilo Ardila[1], Diana Maria Martinez Castillo[1], Ana Maria Calle[1], Carlos Chinchilla[1]

ABSTRACT

Introduction: Hypersensitivity to chemotherapeutic and biological agents has increased in recent years due to their frequent use. Avoidance has been the first line of defense, leading to decreased treatment efficacy and increased adverse events. **Objective:** To characterize the sociodemographic and clinical aspects of patients with hypersensitivity reactions to chemotherapeutic agents who underwent desensitization and biological procedures in a Colombian city. **Methods:** This observational, descriptive, retrospective, multicenter study was conducted in patients with hypersensitivity reactions to chemotherapeutic and biological agents who underwent desensitization. **Results:** In the 14 included patients with a history of hypersensitivity reactions to chemotherapeutic and biological agents (57.1% women; median age 42.5 years), 45 desensitization procedures were performed. The most commonly prescribed drug was rituximab (57%). The skin was the most frequent reaction site (78.6%), and systemic corticosteroids were the most common treatment (78.6%). Breakthrough reactions occurred in 31.1% of the patients and only premedication with corticosteroids was associated with less severe reactions. All cases of desensitization were successful. **Conclusions:** Desensitization to chemotherapeutic and biological agents proved to be a useful and safe tool in a Colombian population.

Keywords: Hypersensitivity, chemotherapeutic agent, biological agent, desensitization.

RESUMO

Introdução: A hipersensibilidade aos agentes quimioterápicos e biológicos aumentou nos últimos anos devido ao seu uso frequente. Evitar tem sido a primeira linha de ação, levando à diminuição da eficácia do tratamento e ao aumento de eventos adversos. **Objetivos:** Caracterizar os aspectos sociodemográficos e clínicos de pacientes com reações de hipersensibilidade a agentes quimioterápicos submetidos a dessensibilização e procedimentos biológicos em uma cidade colombiana. **Métodos:** Foi realizado um estudo observacional, descritivo, retrospectivo e multicêntrico em pacientes com reações de hipersensibilidade a agentes quimioterápicos e biológicos submetidos à dessensibilização. **Resultados:** Foram incluídos 45 procedimentos de dessensibilização em 14 pacientes com histórico de reações de hipersensibilidade a agentes quimioterápicos e biológicos (57,1% mulheres, com mediana de idade de 42,5 anos). O medicamento mais relatado foi o rituximabe (57%). O envolvimento cutâneo foi o mais frequente (78,6%) e os corticosteroides sistêmicos foram o tratamento mais utilizado (78,6%). As reações ocorreram em 31,1% e apenas a pré-medicação com corticosteroides foi associada a uma menor gravidade destas. Todos os casos de dessensibilização foram bem-sucedidos. **Conclusões:** A dessensibilização a agentes quimioterápicos e biológicos provou ser uma ferramenta útil e segura em uma população colombiana.

Descritores: Hipersensibilidade, agentes antineoplásicos, terapia biológica, dessensibilização.

1. Servicio de Alergología de la Universidad de Antioquia – Colombia.

Submitted: Mar 27 2023, accepted: May 27 2023.

Arq Asma Alerg Imunol. 2023;7(2):189-200.

http://dx.doi.org/10.5935/2526-5393.20230025-en

Introduction

Adverse drug reactions are a public health problem,[1] and hypersensitivity reactions comprise 15-20% of these cases.[2] For taxane-based chemotherapeutic agents, a 2%-10% prevalence of hypersensitivity reactions has been reported, while for platinum-based[13] drugs it depends on the number of infusions.[4] The epidemiology of hypersensitivity reactions to biological agents is insufficiently known; the most commonly involved drug is rituximab, for which the prevalence is 5% to 10%.[5]

Chemotherapeutic and biological agents have been increasingly used in recent years, resulting in more hypersensitivity reactions,[6] which can lead to the use of less effective and safer alternatives.[7,8] These patients can benefit from drug desensitization protocols for temporary tolerance.[9]

Although evidence indicates that desensitization is safe, the procedure is not risk-free, and thus should be performed in an appropriate medical environment, with the necessary supplies to manage emergencies, and it should be performed by qualified and trained personnel.[6,10]

Studies have described the results and safety of desensitization to chemotherapeutic agents in 413, 609, and 122 patients.[11-13] An Australian study described 25 procedures with chemotherapeutic and biological agents,[14] and a more recent study reported the results of 69 desensitization procedures.[15] In Latin America, Villarreal et al.[16] described a cohort of patients with reactions to paclitaxel who underwent successful desensitization. However, we could find no information on other therapeutic agents, except as case reports. In Colombia, we found no studies evaluating hypersensitivity reactions to chemotherapeutic and biological agents or desensitization protocols for these drugs.

The primary objective of this study was to characterize the sociodemographic and clinical aspects of patients with hypersensitivity reactions to chemotherapeutic and biological agents who underwent desensitization and treatment in a Colombian city.

Methodology

An observational, multicenter, descriptive study was conducted at the Hospital San Vicente Fundación and the IPS Universitaria, both of which are in Medellín. The secondary objectives were to describe the sociodemographic aspects of the study population; to describe the clinical and paraclinical history of this population; to determine aspects of desensitization, adverse reactions, and the final outcome of the procedure, and finally; to explore the relationship between demographic, clinical and paraclinical aspects according to desensitization, adverse reactions, and procedure outcome.

Data were collected from the medical records of patients with a history of hypersensitivity reaction to chemotherapeutic or biological agents who underwent a desensitization protocol between 2015 and 2020. We assessed the demographic and clinical characteristics of the patients, as well as clinical aspects of the index reaction and desensitization procedure.

For this study, hypersensitivity reactions were considered signs or symptoms produced by an agent normally tolerated by the general population, in this case chemotherapeutic and biological agents, that are unrelated to drug's action and are, thus, unpredictable.[1] Hypersensitivity was not diagnosed by the researchers; the sample included patients who had already been diagnosed by an allergist. The type of hypersensitivity reaction was not differentiated. The Ring-Messmer scale[6] was used to determine reaction severity: mild reactions were considered grade I (affecting only the skin), while all other were considered moderate to severe (grades II-IV).

The index reaction was considered the patient's predictable response to the drug, ie, that for which hypersensitivity was diagnosed. Reactions that occurred during desensitization were considered breakthrough reactions.

Statistical analysis

For descriptive analysis of the sociodemographic, clinical, and paraclinical variables, absolute and relative frequencies and summary indicators, such as median, quartiles, interquartile range, and minimum and maximum values were used. The standard criterion for quantitative variables was determined with the Shapiro-Wilk test.

The likelihood ratio chi-square test and Fisher's exact test were applied to determine the relationship between demographic, clinical, and paraclinical aspects according to desensitization, adverse reactions, and outcome. Cramer's V was used as a measure of effect size. P-values < 0.05 were considered statistically significant.

Ethical aspects

This investigation was based on international ethical principles in accordance with the Declaration of Helsinki and the Nuremberg Code and was approved by the ethics committee of the participating institutions.

Results

Sociodemographic aspects and clinical history

The sample included 14 patients with hypersensitivity reactions to chemotherapeutic and biological agents who underwent desensitization procedures for these drugs. Most patients were women (57.1%) and the median age was 42.5 years.

The drugs that caused the reactions were prescribed for hematological diseases (42%), solid organ neoplasms (28.5%), or autoimmune diseases (28.5%). The majority (64%) of the patients had previously used a chemotherapeutic or biological agent (Table 1).

Characteristics of the index hypersensitivity reaction

The most commonly reported drug reactions were to rituximab (57.1%) and oxaliplatin (28.6%). The median number of reactions per patient was 1, and most (85.7%) were immediate. The skin was the most commonly affected site (78.6%). No patient had a fever or liver or renal involvement. The most commonly used drugs for these reactions were corticosteroids (78.6%) and antihistamines (64.3%).

Serum tryptase measurement was not performed for any patients at the time of the reaction, and a skin test was only performed in 1 patient (Table 2).

Characteristics of the desensitization procedure

A total of 45 desensitization procedures were performed for the 14 included patients, averaging 2.5 procedures per patient. Of the desensitization procedures, 28 (65.1%) were administered using a 3-bag, 12-step protocol, and 9 (20.9%) used a 4-bag, 16-step protocol. All protocols involved solutions with different drug dilutions, beginning with the most dilute solution. Four protocol steps were administered for each bag, increasing the infusion rate every 15 minutes in each step. Premedication was administered in all procedures, the most common of which were antihistamines (97.8%) and corticosteroids (82.2%).

Breakthrough reactions occurred during 14 (31.1%) procedures, in which the skin was the main affected site (92.9%). More than a third (35.7%) of these reactions occurred during step 12. The reactions were treated with antihistamines (85.7%) and systemic corticosteroids (35.7%). All procedures were completed at the full dose and were thus considered successful (Table 3).

Demographic and clinical characteristics according to index reaction

All patients ≥ 45 years of age presented systemic symptoms, compared to 50% of those < 45 years of age (medium effect size; Cramer's V = 0.548). Likewise, among patients with a solid organ neoplasm, 50% of those with a hematologic neoplasm and 75% of those with autoimmune diseases presented systemic reactions (medium effect size; Cramer's V = 0.487). There was no difference in the systemic reaction rate between patients with a history of atopic disease and those with other diseases (Table 4).

All of the patients who had an index reaction to cytarabine and 87.5% of those who had an index reaction to rituximab did so with ≤ 3 doses of the drug , while all of those who had an index reaction to methotrexate or oxaliplatin did so after the third dose. This difference was significant (p = 0.006) and had a large effect size (Cramer's V = 0.863).

Demographic and clinical characteristics according to breakthrough reaction

Among cytarabine desensitization procedures, 83.3% involved a breakthrough reaction, compared to 50% for oxaliplatin and 16.7% for rituximab. These differences were significant and had a moderate effect size (p = 0.007, Cramer's V = 0.524). There was no relationship between systemic symptoms in the index reaction and the occurrence of a breakthrough reaction.

Breakthrough reactions occurred in 75% of the procedures in which corticosteroids were not administered, which was a significant difference with a moderate effect size (p = 0.04; Cramer's V = 0.441). There was also a significant association between breakthrough reactions and desensitization protocols > 6 hours in length (p = < 0.001) (Table 5).

Table 1
Sociodemographic and clinical characteristics of the included patients

		Relative frequency
Sex	Female	57.1% (8)
	Male	42.9% (6)
Age groups	Age < 45	40% (18)
	Age ≥ 45	60% (27)
Residential area	Rural	7.1% (1)
	Urban	92.9% (13)
Race	Mestizo (Mixed race)	100% (14)
Asthma	Yes	14.3% (2)
Rhinitis	Yes	14.3% (2)
Conjunctivitis	Yes	7.1% (1)
Dermatitis	Yes	0
HBP	Yes	14.3% (2)
Diabetes mellitus	Yes	7.1% (1)
Cardiovascular disease	Yes	7.1% (1)
Pulmonary disease	Yes	14.3% (2)
Liver disease	Yes	7.1% (1)
Renal disease	Yes	21.4%
Endocrine disease	Yes	7.1% (1)
Psychiatric disease		7.1% (1)
Underlying disease	Hematologic neoplasm [a]	42.8% (6)
	Solid organ neoplasm [b]	28.5% (4)
	Autoimmune disease [c]	28.5% (4)

[a] Burkitt's leukemia, acute myeloid leukemia, B-cell lymphoma, non-Hodgkin's lymphoma, Waldeström macroglobulinemia.
[b] Colon cancer, cholangiocarcinoma, gastric cancer.
[c] Dermatomyositis, SLE, optic neuritis, primary immune thrombocytopenia.

Table 2
Characteristics of the index hypersensitivity reactions

		Relative frequency
Drug	Cytarabine	7.1% (1)
	Methotrexate	7.1% (1)
	Oxaliplatin	28.6% (4)
	Rituximab	57.1% (8)
No. of reactions [a]	1 (1) [1; 3]	
Latency time	< 1 hour	85.7% (12)
	> 6 hours	14.3% (2)
Dose at which the reaction occurred [a]	3 (2) [1; 9]	
Clinical manifestations	Skin	78.6% (11)
	Respiratory	57.1% (8)
	Gastrointestinal	14.3% (2)
	Cardiovascular	28.6% (4)
	Neurological	7.1% (1)
Tryptase measurement	No	100%
Skin test	Positive	0
	Negative	7.1% (1)
	Not performed	92.9% (13)
Reaction treatment	Adrenaline	35.7% (5)
	Antihistamine	64.3% (9)
	Corticosteroid	78.6% (11)
	Anti-H2	4.4% (2)
	LTRA	0
	EVF	28.6% (4)
	Analgesics or antipyretics	7.1% (1)
	Beta-2 agonists	0
	Oxygen	28.6% (4)

[a] Results are presented as median (interquartile range) [minimum value; maximum value].
LTRA = leukotriene receptor antagonist, EVF = endovenous fluids.

Table 3
Aspects of desensitization, breakthrough reactions, and final outcome of the procedure

		Relative frequency
Number of desensitization procedures per patient [a]	2.5 (3) [1; 6]	
Regimen used	3-bag, 12-step	65.1% (28)
	4-bag, 16-step	20.9% (9)
	Other	14% (6)
Site of procedure	Inhospital	82.2% (37)
	Emergency services	2.2% (1)
	SCU	4.4% (2)
	Outpatient department	11.1% (5)
Procedure duration (hours) [a]	6.5 (2) [4.5; 10]	
Premedication	Yes	100% (45)
Used premedication	Corticosteroid	82.2% (37)
	Antihistamine	97.8% (44)
	LTRA	8.9% (4)
	Analgesics	24.4% (11)
	Anxiolytic	4.4% (2)
	LEV	0
Breakthrough reaction	Yes	31.1% (14)
	No	68.9% (14)
Step in which the reaction occurred	4	7.1% (1)
	12	35.7% (5)
	15	7.1% (1)
	>24 hours	35.7% (5)
	No information	14.2 (2)
Clinical manifestations of the breakthrough reaction	Skin	92.9% (13)
	Respiratory	0
	Cardiovascular	7.1% (1)
	Gastrointestinal	14.3% (2)
	Renal	0
	Liver	0
	Neurological	0
	Fever	7.1% (1)
Breakthrough reaction treatment	Adrenaline	0
	Antihistamine	85.7% (12)
	Corticosteroid	35.7% (5)
	LTRA	7.1% (1)
	Analgesics or antipyretics	14.3% (2)
	Oxygen	0
	EVF	21.4% (3)
	Beta-2 agonist	0
Procedure results	Successful	100% (45)

[a] Results presented as median (interquartile range) [minimum value; maximum value].
LTRA = leukotriene receptor antagonist, EVF = endovenous fluids, SCU = special care unit.

Table 4
Demographic and clinical characteristics according to index reaction

		Systemic involvement in index reaction		p-value[a]	Difference in proportions (95%CI)	Cramer's V
		Yes	No			
Sex	Female	6 (75.0%)	2 (25.0%)	0.999	0.0833 (-0.399 to 0.565)	0
	Male	4 (66.7%)	2 (33.3%)			
Age groups	Age < 45	4 (50.0%)	4 (50.0%)	0.085	0.500 (0.154-0.846)	0.548
	Age ≥ 45	6 (100%)	0 (0%)			
Involved drug	Cytarabine	0 (0.0%)	1 (100.0%)	0.043	NA	0.689
	Methotrexate	0 (0.0%)	1 (100.0%)			
	Oxaliplatin	4 (100.0%)	0 (0.0%)			
	Rituximab	6 (75.0 %)	2 (25.0%)			
Treated with adrenaline	Yes	4 (80.0%)	1 (20.0%)	0.999	0.133 (-0.133 to 0.600)	0.141
	No	6 (66.7%)	3 (33.3%)			
Treated with antihistamines	Yes	1 (50.0%)	1 (50.0%)	0.505	-0.250 (-0.985 to 0.485)	0.194
	No	9 (75.0%)	3 (25.0%)			
Treated with corticosteroids	Yes	9 (81.8%)	2 (18.2%)	0.176	0.485 (-0.0952 to 1.00)	0.440
	No	1 (33.3%)	2 (66.7%)			
Treated with anti-H2	Yes	1 (50.0%)	1 (50.0%)	0.505	-0.250 (-0.985 to 0.485)	0.194
	No	9 (75.0%)	3 (75.0%)			
Treated with analgesics and/or antipyretics	Yes	1 (100.0%)	0 (0.0%)	0.999	0.308 (0.0568-0.559)	0.175
	No	9 (62.0%)	4 (30.8%)			
Treated with oxygen	Yes	4 (100.0%)	0 (0.0%)	0.251	0.400 (0.0964-0.704)	0.400
	No	6 (60.0%)	4 (40.0%)			
Treated with EVF	Yes	4 (100.0%)	0 (0.0%)	0.251	0.400 (0.0964-0.704)	0.400
	No	6 (60.0%)	4 (40.0%)			

[a] Fisher's exact test.
EVF = endovenous fluids; NA = not applicable.

Table 5
Demographic and clinical characteristics according to breakthrough reaction

		Breakthrough reaction				
		Yes	No	p-value[a]	Difference in proportions (95%CI)	Cramer's V
Sex	Female	8 (30.8%)	18 (69.2%)	0.954	-0.00810 (-0.282 to 0.266)	0.00864
	Male	6 (31.6%)	13 (68.4%)			
Age group	Age < 45	6 (33.3%)	12 (66.7%)	0.793	-0.0370 (-0.315 to 0.241)	0.0392
	Age ≥ 45	8 (29.6%)	19 (70.4%)			
Previous use of chemotherapeutic or biological agents	Yes	7 (28.0%)	18 (72.0%)	0.615	-0.0700 (-0.343 to 0.203)	0.0751
	No	7 (35.0%)	13 (65.0%)			
Site of procedure	Inhospital	13 (35.1%)	24 (64.9%)	0.050	NA	0.354
	Emergency services	1 (100.0%)	0 (0.0%)			
	SCU	0 (0.0%)	2 (100.0%)			
	Outpatient department	0 (0.0%)	5 (100.0%)			
Corticosteroid	Yes	8 (21.6%)	29 (78.4%)	0.004	-0.534 (-0.862 to -0.206)	0.441
	No	6 (75.0%)	2 (25.0%)			
Antihistamine	Yes	14 (31.8%)	30 (68.2%)	0.385	0.318 (-0.181 to -0.456)	0.101
	No	0 (0.0%)	1 (100.0%)			
LTRA	Yes	2 (50.0%)	2 (50.0%)	0.409	0.207 (-0.302 to -0.717)	0.127
	No	12 (29.3%)	29 (70.7%)			
Analgesic	Yes	2 (18.2%)	9 (81.8%)	0.270	-0.171 (-0.450 to 0.108)	0.159
	No	12 (35.3%)	31 (64.7%)			
Anxiolytic	Yes	0 (0.0%)	2 (100.0%)	0.216	-0.326 (-0.466 to -0.186)	0.145
	No	14 (32.6%)	29 (67.4%)			
Duration	≤ 6 hours	1 (7.1%)	17 (58.6%)	< 0.001	-0.515 (-0.739 to -0.290)	0.489
	> 6 hours	13 (92.9%)	12 (41.4%)			

[a] Likelihood ratio.
LTRA = leukotriene receptor antagonist, NA = not applicable, SCU = special care unit.

Demographic and clinical characteristics according to systemic symptoms in breakthrough reactions

Systemic symptoms and baseline disease were significantly associated, having a large effect size. Among patients with solid organ neoplasms, 75% had a systemic breakthrough reaction, compared to 15% of those with hematologic neoplasms and 0% of those with an autoimmune disease (p = 0.039; Cramer's V = 0.661).

Breakthrough reactions with systemic symptoms occurred in 75% of the procedures for oxaliplatin, compared to 0% for rituximab. This difference was significant and had a large effect size (p = 0.008; Cramer's V = 0.791).

Breakthrough reactions with systemic symptoms occurred in 44% of the first 2 procedures and none occurred after the third procedure. This difference was significant and had a moderate effect size (p = 0.036; Cramer's V = 0.471) (Table 6).

Table 6
Distribution of clinical aspects according to systemic involvement in the breakthrough reaction

		Systemic involvement in the breakthrough reaction		p-value[a]	Difference in proportions (95%CI)	Cramer's V
		Yes	No			
Underlying disease	Solid organ neoplasm	3 (75.0%)	1 (25.0%)	0.039	NA	0.661
	Hematologic neoplasm	1 (14.3%)	6 (85.7%)			
	Autoimmune disease	0 (0.0%)	3 (100.0%)			
Drug	Cytarabine	1 (20.0%)	4 (80.0%)	0.064	NA	0.474
	Methotrexate	0 (0.0%)	0 (0.0%)			
	Oxaliplatin	3 (75.0%)	1 (25.0%)			
	Rituximab	0 (0.0%)	5 (100%)			
Regimen	3-bag, 12-step	0 (0.0%)	3 (100.0%)	0.059	NA	0.548
	4-bag, 16-step	4 (50.0%)	4 (50.0%)			
	Other	0 (0.0%)	3 (100%)			
Systemic involvement in index reaction	Yes	3 (37.5%)	5 (62.5%)	0.383	-0.208 (-0.657 to 0.241)	0.228
	No	1 (16.7%)	5 (83.3%)			
Number of desensitization procedures	≤ 2	4 (44.4%)	5 (55.6%)	0.036	-0.444 (-0.769 to -0.120)	0.471
	> 2	0 (0.0%)	5 (100%)			

[a] Likelihood ratio.
NA = not applicable.

Discussion

The present sample included 45 desensitization procedures with chemotherapeutic and biological agents. Like other studies, our patients were mostly women, possibly due to the large number of patients with gynecologic malignancies. In addition, biological agents are an important treatment for rheumatological and autoimmune diseases, which are more frequent in women.[11,19]

The median patient age was also similar to other studies, although we found that all patients > 45 years had systemic symptoms in the index reaction, unlike in other studies, where none described a relationship between age and index reaction severity.[11,15]

The youngest patient in our sample (6 years), had a hypersensitivity reaction to rituximab and underwent 4 desensitization procedures with a 12-step protocol. No breakthrough reactions occurred in any of these procedures. Diley et al. described 17 desensitization procedures with rituximab, also using a 12-step protocol in 3 children (aged 14 years, 7 years, and 23 months). Because the younger 2 had breakthrough reactions, a modified protocol was used with an infusion rate ≤ 2 mg/kg/h.[20]

Similar to our findings, other authors have reported that these drugs were mainly prescribed (70-94%) for neoplastic diseases.[15,21] The most frequently reported neoplasms in similar studies are ovarian and breast cancer,[13] in contrast to hematological neoplasms in our study.

Most of the rituximab hypersensitivity reactions in our sample occurred in the first treatment cycles, which is consistent with the literature.[15] Up to 50% of the reactions to this drug occur during the first exposure, which suggests a cytokine-releasing endotype.[22] Moreover, reactions to oxaliplatin occurred after the fourth exposure, which has been reported in other studies.[13] This can be explained by the fact that most hypersensitivity reactions to platinum-based drugs are IgE-mediated.[23,24]

Most reactions were immediate; only 2 patients had delayed reactions: one with a maculopapular rash due to cytarabine and another with a fixed drug eruption due to methotrexate. Skin lesions 6 to 12 hours after administration are typical of hypersensitivity to cytarabine.[25,26] On the other hand, hypersensitivity reactions to methotrexate are rare, and the most common are IgE-mediated.[27]

Regarding reaction severity, in our results, as well as the literature, most index reactions are moderate or severe (64.3 to 87.9%),[19,21] with skin and respiratory symptoms being the most common symptoms. However, another study found that respiratory (80.5%) and cardiovascular (58.8%) symptoms were the most common types.[15]

None of our patients were tested for biomarkers, such as serum tryptase and IL-6, and only 1 patient, who reacted to methotrexate, was given had a patch test (the results of which were negative). Measuring these biomarkers and performing skin tests is important for phenotyping patients. Elevated tryptase levels during the reaction are associated with an IgE-mediated phenotype,[28] and IL-6 values above the upper threshold are related to cytokine-release.[30] Skin testing, however, has been proposed as a way to stratify risk and guide treatment.[31]

The most widely applied desensitization protocol for chemotherapeutic and biological agents was developed at the Brigham and Women's Hospital (Boston, MA, USA) and involves 3 bags and 12 steps.[11] In our study, 28 procedures were of this type, while 9 were 4-bag, 16-step protocols. The latter type was also described by the Brigham and Women's Hospital group in that they recommended adding steps and modifying the final rate to the original protocol to increase safety.[23] Recently, a 1-bag, 11-step desensitization protocol was tested in 434 procedures, with an efficacy of 99.5% and a breakthrough reaction rate of 49%.[21]

All desensitization procedures in our study involved premedication. Only corticosteroid use was associated with a lower breakthrough reaction rate. We could find no comparable data in the literature about this phenomenon. Current recommendations suggest selecting the premedication according to the symptoms presented in the index reaction.[10]

Breakthrough reactions occurred in 31% of the procedures in our sample. In the literature, breakthrough reactions have been reported in 13% to 39% of desensitization procedures[11,114,15] Reactions generally occur during the final steps of the protocol,[11] which corroborates our finding that most reactions occurred in step 12.

Breakthrough reaction severity was associated with drug type. There was a high percentage of moderate to severe reactions to oxaliplatin, whereas there were only mild reactions to rituximab. Accordingly, the literature reports more severe breakthrough reactions to platinum-based drugs than to biological agents.[19] We also found a relationship between protocol type

and breakthrough reaction severity. In the 16-step protocol, 50% of the reactions were moderate to severe, while in the 12-step protocol the reactions were mild. This may be because patients indicated for the longer protocol had a higher risk in baseline stratification.

In patients who underwent multiple desensitization procedures, although the frequency of breakthrough reactions did not decrease as more procedures were performed, the severity did. Other studies have reported that in addition to severity, the frequency of reactions also decreases.[11,13]

All desensitization procedures in our study were successful. In some cohorts, lower success rates have been obtained (84%[14] and 98%[19]), while others report complete success.[11]

The retrospective nature of this study can be considered a limitation, as can the small sample and number of desensitization protocols. This is due to the fact that these procedures are still little known in our work environment and are only performed at certain institutions. Finally, none of the patients were tested for biomarkers and only 1 underwent skin testing, which are important diagnostic and therapeutic tools.

The study's main advantage is that it is the first, to the best of our knowledge, in Latin America to describe the characteristics of desensitization procedures in patients with hypersensitivity reactions to chemotherapeutic and biological agents. We hope that it leads to further research on the topic.

Conclusion

Desensitization protocols are an effective alternative in patients with hypersensitivity reactions to chemotherapeutic and biological agents and, although they are not risk-free procedures, they are safe if performed under adequate conditions by trained personnel. We found that corticosteroid administration was associated with fewer reactions during the procedure, which would be an interesting topic for future research.

Acknowledgments

The authors would like to thank Dr. Catalina Gómez and Dr. Susana Uribe for their suggestions, which enriched our study, the IPS Universitaria and Hospital San Vicente Fundación for allowing us to develop this study in their institutions, and the Universidad de Antioquia, especially the Clinical Allergology program, including the professors, residents, and nursing and administrative staff.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Juan Camilo Ardila-Herrera
E-mail: caardhe@hotmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

COVID-19 vaccination safety in patients with hymenoptera venom allergy referred by primary health care

Segurança da vacinação contra a COVID-19 em doentes referenciados dos cuidados de saúde primários por alergia ao veneno de himenópteros

Ricardo José Brás[1], Joana Cosme[2,3], Rita Brás[2], Elisa Pedro[2], Amélia Spínola Santos[2,3]

ABSTRACT

Introduction: Despite numerous reports of hypersensitivity reactions to COVID-19 vaccination, anaphylaxis is rare. Although hypersensitivity reactions to hymenoptera venom are the third most common cause of anaphylaxis in Portugal, they don't appear to enhance the risk of anaphylactic reaction to COVID-19 vaccination. **Objectives:** To assess the safety of COVID-19 vaccination in patients with a history of hymenoptera venom allergy. **Methods:** This retrospective observational study included patients with hymenoptera venom allergy referred by primary health care to the Immunoallergology Outpatient Clinic of a tertiary hospital between January and December 2021 to stratify the risk of hypersensitivity reactions to the SARS-CoV-2 vaccine. **Results:** A total of 18 patients were included: 72% women; mean age 61 (SD, 18 [range 21-89]) years. One-third of all reported reactions to hymenoptera venom were large and local. Topical systemic symptoms of anaphylaxis were mucocutaneous (33%), respiratory (28%), cardiovascular (33%) and gastrointestinal (11%). The honeybee was the most frequently involved hymenoptera species (61%). The basal tryptase levels of 3 patients were above the established cut-off (11.4 ng/mL) and they were formally indicated for vaccination in a hospital setting. Concerning the vaccination process, 46 doses were administered to the 18 patients and no reactions were recorded. Only 5 patients were vaccinated in a hospital environment; the rest were referred to primary health care centers. Patients with confirmed or suspected mastocytosis were premedicated with anti-H1 and anti-H2 antihistamines, as well as montelukast, the day before and on the day of vaccination. **Conclusions:** COVID-19 vaccination is safe for patients with hypersensitivity to hymenoptera venom. The risk assessment protocol effectively designated patients to primary or secondary/tertiary health care.

Keywords: Allergy, anaphylaxis, COVID-19 vaccination, hypersensitivity to hymenoptera venom, tryptase.

RESUMO

Introdução: As reações de hipersensibilidade após vacinação contra a COVID-19 têm vindo a ser descritas, embora a anafilaxia seja rara. A hipersensibilidade ao veneno de himenópteros constitui a terceira causa mais frequente de anafilaxia em Portugal, embora não pareça aumentar o risco de anafilaxia à vacinação contra a COVID-19. **Objetivos:** Avaliar a segurança da vacinação contra a COVID-19 em doentes com história de alergia ao veneno de himenópteros referenciados dos Cuidados de Saúde Primários (CSP). **Métodos:** Estudo observacional retrospectivo com inclusão dos doentes com alergia ao veneno de himenópteros referenciados pelos CSP ao serviço de Imunoalergologia, para estratificação do risco de reações de hipersensibilidade à vacina contra o SARS-CoV-2, entre janeiro e dezembro de 2021. **Resultados:** No total, incluíram-se 18 doentes, 72% do sexo feminino, média de idades de 61±18 [21-89] anos. Na caracterização do tipo da reação ao veneno de himenópteros, as reações locais exuberantes corresponderam a 33% de todas as reações referidas. Quanto a sintomas sistêmicos de anafilaxia, foram referidos sintomas mucocutâneos (33%), respiratórios (28%), cardiovasculares (33%) e gastrointestinais (11%). A abelha foi o inseto mais frequentemente implicado (61%). Relativamente aos valores de triptase basal, 3 doentes apresentaram níveis acima do *cut-off* estabelecido de 11,4 ng/mL, tendo indicação formal para iniciar esquema de vacinação em meio hospitalar. Durante o processo vacinal registrou-se um total de 46 administrações em 18 doentes, todas sem intercorrências. Apenas 5 doentes foram vacinados em meio hospitalar, tendo sido os restantes encaminhados para os CSP. Os doentes com mastocitose confirmada ou suspeita foram submetidos à pré-medicação com anti-histamínico anti-H1 e anti-H2, bem como montelucaste, na véspera e no dia da vacinação. **Conclusões:** A vacinação contra a COVID-19 é segura em doentes com reação de hipersensibilidade ao veneno de himenópteros. O protocolo utilizado mostrou ser eficaz na segregação de doentes entre CSP e cuidados secundários/terciários.

Descritores: Alergia, anafilaxia, hipersensibilidade ao veneno de himenópteros, triptase, vacinação COVID-19.

1. Group of North Lisbon Health Centers, Dona Amélia de Portugal Family Health Unit – Lisbon, Portugal.
2. North Lisbon University Hospital Center, Immunoallergology Department, Hospital de Santa Maria – Lisbon, Portugal.
3. University of Lisbon Medical School, University Clinic of Immunoallergology – Lisbon, Portugal.

Submitted Apr 18 2023, accepted July 01 2023.

Arq Asma Alerg Imunol. 2023;7(2):201-8.

http://dx.doi.org/10.5935/2526-5393.20230026-en

Introduction

Vaccination is a key type of primary prevention in medicine, being considered one of the most successful public health strategies.[1] Since the beginning of the SARS-CoV-2 pandemic, the scientific community has joined efforts to effectively reduce the morbidity and mortality associated with this infection, creating new types of treatments in record time. However, the most promising results have been obtained with vaccine development.[2]

Given the speed with which vaccines were produced and approved, questions were raised not only about their efficacy but also about their safety.[3] However, there was a consensus among international organizations regarding the approval of several types of vaccines against COVID-19. Currently, 5 vaccines are approved by the European Medicines Agency (EMA) for use in Europe, as well as by the National Institute of Pharmacy and Medicines (INFARMED) in Portugal: viral vector vaccines Vaxzevria® (AstraZeneca) and Janssen® (Johnson&Johnson), mRNA vaccines Comirnaty® (Pfizer-BioNTech) and Spikevax® (Moderna), and the SARS-CoV-2 recombinant spike protein nanoparticle vaccine Nuvaxovid® (Novavax).[4,5]

In the phase 3 trials of these vaccines, there was no report of any case of anaphylaxis, but participants with a history of allergic reaction to any excipient of the vaccine in question were previously excluded, which raised some concerns about their safety in patients with known allergies.[6,7] Since then, multiple studies have been published pointing to the safety of COVID-19 vaccines, with an incidence of anaphylaxis of approximately 7.91-10.67 cases per million doses.[8,9] This incidence is higher than that reported for some commonly administered vaccines, such as influenza (0.8 per million doses) (1), but lower than that reported for some National Immunization Program vaccines, such as the human papilloma virus vaccine (13.65 per million doses) or the measles, mumps, and rubella vaccine (19.8 per million doses).[9] This fact does not exclude the need for health professionals to be aware of possible allergic reactions associated with vaccination, as well as their correct reporting, namely anaphylaxis.[1]

Referral criteria for hospital-based vaccination have changed with the increase in medical knowledge and publication of studies in the field. All protocols are flexible and require individual consideration. Regulations have been developed, according to which patients with mastocytosis should be referred to in-hospital vaccination.[10-13]

According to recent studies conducted by Gaspar et al, in the last decade, insect-sting anaphylaxis was the third most common cause of anaphylaxis in Portugal, accounting for 7.4% of all cases, after food-induced (48.2%) and drug-induced anaphylaxis (36.9%).[14,15] The diagnosis of mastocytosis in patients with Hymenoptera venom allergy is a risk factor for episodes of anaphylaxis.[16] In this context, baseline serum tryptase measurement in patients with Hymenoptera venom anaphylaxis plays a decisive role in choosing the referral site for SARS-CoV-2 vaccination, despite the fact that its ordering is not reimbursed by the National Health Service when it is prescribed in the primary care setting. However, several studies have already demonstrated that these patients can be safely vaccinated in a non-hospital setting, under a premedication protocol and 30-minute medical surveillance after vaccination.[6,17,18]

The current study aimed to evaluate the safety of COVID-19 vaccines in patients referred from primary care with Hymenoptera venom allergy, analyzing the importance of baseline serum tryptase measurement in the risk stratification of these patients.

Methods

Study Design , population, and data collection

We conducted a retrospective observational study of patients referred from primary care to the immunoallergology clinic for risk assessment of severe allergic reactions to SARS-CoV-2 vaccines due to a history of Hymenoptera sting reactions, between January and December 2021.

The patients were evaluated remotely by telephone calls and/or in a face-to-face consultation when it was not possible for the physician to have a correct perception of the patient's medical history without a physical examination.

The definition of anaphylaxis was based on the European Academy of Allergy and Clinical Immunology (EAACI) criteria,[19] which define anaphylaxis as a severe, potentially life-threatening systemic hypersensitivity reaction characterized by a rapid onset that may include mucocutaneous, respiratory, cardiovascular, or gastrointestinal manifestations.

Systemic hypersensitivity reactions were categorized according to the Mueller classification.[20] This classification divides reactions into 4 grades

according to their severity. Grade I systemic reaction is characterized by itching, urticaria, anxiety, and/or malaise. Grade II reaction includes any of the grade I symptoms plus 2 or more of the following: dizziness, nausea and vomiting, diarrhea, abdominal pain, angioedema, and/or a feeling of tightness in the chest. Grade III reaction includes grade I or II symptoms plus at least 2 of the following: dyspnea, dysarthria, wheezing, stridor, hoarseness, prostration, confusion, and/or a feeling of impending doom. Finally, grade IV reaction includes grade I, II, or III symptoms plus at least 2 of the following: loss of consciousness, urinary and fecal incontinence, and/or cyanosis.[19]

Data were collected from the patients' hospital medical records and the Health Data Platform in order to include relevant information about the primary care setting, as well as post-vaccination outcomes of patients referred to a non-hospital setting after risk vaccination.

Risk stratification protocol for hypersensitivity reactions

Risk stratification of severe hypersensitivity reaction to COVID-19 vaccines was performed in accordance with the protocol of the Immunoallergology Department, based on the regulations of the Directorate-General for Health and national and international guidelines.[16-18,20-24] This protocol is summarized in Table 1.

Baseline tryptase measurement was required at the first COVID-19 screening appointment for all patients referred for suspected Hymenoptera venom anaphylaxis and whose baseline tryptase level was unknown. Patients with levels lower than 11.4 ng/mL were considered at low risk and referred to out-of-hospital vaccination, whereas patients with tryptase levels greater than or equal to 11.4 ng/mL were referred to in-hospital vaccination, with further investigation to exclude mastocytosis or mast cell activation syndrome. These patients were premedicated with H1 and H2 antihistamines 1 hour before vaccination, as well as with montelukast 24 hours and 1 hour before vaccination.[6]

Results

In 2021, 19 patients with suspected Hymenoptera venom allergy were referred from primary care to the immunoallergology clinic for risk stratification of severe hypersensitivity reaction to COVID-19 vaccines, 1 of whom was excluded due to vaccine refusal. Table 2 shows the demographic and clinical characteristics of the study population. A total of 18 patients were included in the study, and the majority was female (72%). The mean age was 61 (SD, 18) years, with a minimum age of 21 years and a maximum age of 89 years.

Regarding concomitant immunoallergic pathologies, the most prevalent was allergic rhinitis, with 33% of patients reporting this diagnosis. Other reported pathologies were asthma (n = 2, 11%), mastocytosis (n = 1, 6%), and chronic urticaria (n = 2, 11%). Non-allergic pathologies, such as hypertension, heart failure, dyslipidemia, and chronic obstructive pulmonary disease, were reported by 22% of patients.

In the characterization of the reaction to Hymenoptera venom, 6 patients reported only exuberant local reaction. According to the Mueller classification, the most frequent systemic reaction was grade III, occurring in 5 patients (Table 2). Regarding the remaining systemic reactions, there was 1 grade I reaction, 2 grade II reactions, and 4 grade IV reactions. Honeybee was the species of Hymenoptera most commonly involved (61%), but there were also reports of several cases related to wasps (28%). The causative agent of the reaction could not be determined in the remaining cases (n=2, 11%).

Of the 18 patients with a history suggestive of hypersensitivity to Hymenoptera venom, 3 (17%) had baseline tryptase levels above 11.4 ng/mL and were referred to in-hospital vaccination. These 3 patients had a history of anaphylaxis, representing 25% of anaphylactic reactions to Hymenoptera venom. All patients were also asked about possible previous severe hypersensitivity reactions, with 33% reporting a history of drug-induced anaphylaxis, with nonsteroidal anti-inflammatory drugs corresponding to half of the cases and intravenous contrast to 6%. Food-induced (11%) and idiopathic anaphylaxis (11%) were also reported.

Of the patients with Hymenoptera venom anaphylaxis, 3 had already completed 5 years of bee venom immunotherapy, showing no further anaphylactic reactions to stings after completion of vaccination. The remaining patients were referred to specialist consultations for Hymenoptera venom allergy, but only 2 remained in follow-up and agreed to start immunotherapy.

After risk assessment and stratification of all patients in the immunoallergology clinic, 5 patients

(28%) were vaccinated in a hospital setting, 3 due to elevated baseline tryptase levels (one of them with a confirmed diagnosis of mastocytosis) and 2 due to other risk factors (idiopathic anaphylaxis in one patient, and a history of multiple drug allergies in the other), all of them under the premedication protocol. The remaining patients were referred to health centers or corresponding immunization centers for vaccination.

Overall, 11 vaccines were administered in a hospital setting and 35 in a non-hospital setting, as shown in Table 3. No complications were reported in any of the cases. Given the absence of hypersensitivity reactions, 3 of the patients who initially received the Comirnaty® vaccine in the hospital setting were able to proceed with their vaccine schedule at the immunization center on medical advice. This decision to proceed with out-of-hospital vaccination was based

Table 1
Risk stratification protocol for severe reaction to define the place for administration of the COVID-19 vaccine[16-19,21-23]

Risk of severe hypersensitivity reaction to the vaccine	Place for vaccination	Clinical diagnosis
Low risk	Vaccination at the Immunization Center	– Allergic rhinitis – Controlled asthma – Atopic dermatitis – Controlled chronic urticaria – Hereditary angioedema – Latex allergy/anaphylaxis – Hymenoptera venom allergy/anaphylaxis with normal tryptase levels – Food allergy/anaphylaxis
Intermediate-high risk	Hospital-based vaccination	– Anaphylaxis after vaccination – Anaphylaxis to multiple classes of drugs (> 2 drug classes), with tolerance of drugs containing polyethylene glycol – Anaphylaxis of unknown etiology – Hymenoptera venom allergy with elevated tryptase levels – Mastocytosis and/or mast cell activation syndromes
High risk	Investigation by immunoallergology	– History of severe hypersensitivity reaction to any of the components of COVID-19 vaccines – Prior hypersensitivity reaction to a COVID-19 vaccine

on the successful administration of the first dose in the hospital setting and on the growing evidence of the safety of COVID-19 vaccines in patients with mastocytosis.[6] All patients vaccinated in a hospital setting received premedication. No adverse allergic reactions were reported in patients vaccinated in the hospital setting, nor in those vaccinated in the primary care setting.

Discussion

The current retrospective observational study demonstrated the safety of SARS-CoV-2 vaccines in patients referred from primary care with a history of Hymenoptera venom allergy, including patients with elevated baseline serum tryptase levels.

One patient was excluded from our initial population due to vaccine refusal, for a total of 18 patients aged

Table 2
Population characteristics – demographic and clinical data related to Hymenoptera sting reaction

Total (nº)	**18**
Age years (mean±SD [min-max])	61±18 [21-89]
Sex (n (%))	
Female	13 (72)
Type of reaction (n (%))	
Exuberant local reaction	6 (33.3)
Systemic reaction (Mueller classification) (20)	
Grade I	1 (5.6)
Grade II	2 (11.1)
Grade III	5 (27.8)
Grade IV	4 (22.2)
Species of Hymenoptera involved (n (%))	
Bee	11 (61.1)
Wasp	5 (27.8)
Unknown	2 (11.1)
Tryptase level (ng/mL)	
Number of patients ≥ 11.4	3 (16.7)
Number of patients < 11.4	7 (38.9)
Number of patients undetermined	8 (44.4)
Mean (±SD)	10.8±8.7
Systemic mastocytosis (n (%))	
Confirmed	1 (5.6)
Under investigation	2 (11.1)
Excluded	15 (83.3)

SD = standard deviation.

21 to 89 years being vaccinated. A total of 35 vaccines were administered in a non-hospital setting, in 16 patients, and 11 vaccines in a hospital setting, in 5 patients, without complications. In addition, no complications were reported in the 3 patients who were initially vaccinated in a hospital setting and then proceeded with their vaccine schedule in a non-hospital setting. This fact demonstrates the effectiveness of the applied risk stratification protocol, as well as of the premedication regimen.

In patients with suspected or confirmed mastocytosis, the first dose was always administered in a hospital setting. However, the EAACI has recently released a position paper stating that there is no evidence for an increased risk of hypersensitivity reactions in the subgroup of patients with Hymenoptera venom allergy or in the subgroup of stable patients with mastocytosis.[25] In both cases, there is an indication for out-of-hospital vaccination under supervision for 30 minutes after vaccination,

Table 3
Characterization of the vaccination schedule of the study patients

Patient	In-hospital vaccination			Out-of-hospital vaccination		
	1st dose	2nd dose	3rd dose	1st dose	2nd dose	3rd dose
A	–	–	–	VAX	VAX	COM
B[a]	COM	COM	–	–	–	COM
C	COM	COM	–	–	–	COM
D[a]	COM	COM	COM	–	–	–
E	–	–	–	COM	COM	COM
F	–	–	–	SPI	SPI	–
G	–	–	–	COM	COM	–
H	–	–	–	COM	COM	COM
I	COM	–	–	–	COM	–
J	–	–	–	VAX	VAX	COM
K	–	–	–	COM	COM	–
L[a]	COM	COM	COM	–	–	–
M	–	–	–	COM	COM	–
N	–	–	–	COM	COM	COM
O	–	–	–	COM	COM	–
P	–	–	–	VAX	VAX	COM
Q	–	–	–	COM	COM	–
R	–	–	–	COM	COM	–
TOTAL	11	35				

[a] Patients with tryptase levels above the defined cut-off of 11.4 ng/mL.
COM = Comirnaty® (Pfizer vaccine), VAX = Vaxzevria® (AstraZeneca vaccine), SPI = Spikevax® (Moderna vaccine).

and patients with confirmed mastocytosis should receive a premedication regimen.

In this context, Rama et al recently published 2 articles that support the safety of COVID-19 vaccines in patients with mastocytosis, underscoring the need of a premedication regimen.[6,18] Numerous other studies have similarly demonstrated the safety of COVID-19 vaccines.[26-32]

Regarding the elevated baseline serum tryptase levels in some patients in our sample, it is important to note that these levels alone do not lead to the diagnosis of mastocytosis. Tryptase levels above 20 ng/mL, in the absence of concomitant pathologies that can explain levels of this magnitude, are only a minor criterion for the diagnosis of systemic mastocytosis.[33] Serum tryptase measurement is not a routinely ordered test in primary care and is not reimbursed by the National Health Service. Therefore, being unaware of that, many patients with a history of anaphylaxis were referred, in whom baseline serum tryptase levels had never been measured. Despite not meeting the referral criteria for hospital-based COVID-19 vaccination (Table 1),[21] the authors consider that the referral had the added value of raising awareness for this diagnosis and the importance of referring patients with Hymenoptera sting anaphylaxis to specialist immunoallergology consultation.

It is imperative to improve communication between primary care and secondary/tertiary care, as well as to work on the continuous improvement of referral criteria in this and all areas of immunoallergology, so that physicians can work in partnership with patients for the benefit of both, reducing the burden on secondary/tertiary care. We also highlight the importance of gaining knowledge of the diagnostic criteria for anaphylaxis, an often underdiagnosed and undertreated condition, which is potentially life-threatening and requires immediate treatment with intramuscular epinephrine to prevent progression to multiple organ failure.[34]

This study has some limitations, including the small sample size (n = 18), which limits the extrapolation of results, requiring further studies with larger sample sizes to obtain statistically relevant data. Another limitation is the retrospective design, given the possible absence of some information in the medical records. However, this limitation is considered of little relevance, since it was possible to obtain virtually all the data required for the study. In addition, the fact that the diagnosis of Hymenoptera venom allergy was considered only presumptive, based on a suggestive medical history, when deciding on the risk stratification. No skin tests or specific IgE assays for the suspected Hymenoptera venom were performed in the initial screening phase given the urgency of deciding on the place for vaccination. Nevertheless, the authors consider that the current study provides important information about the safety of COVID-19 vaccines in patients with Hymenoptera venom allergy.

Conclusions

COVID-19 vaccination is safe in patients with a history of severe hypersensitivity reaction to Hymenoptera venom and can be conducted in the primary care setting, with rare exceptions. The risk stratification protocol for severe hypersensitivity reactions applied in this study demonstrated to be effective in identifying patients to be vaccinated in a hospital setting. We highlight the importance of continuous improvement of referral criteria and protocols, as well as of communication between primary care and secondary/tertiary care.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Ricardo José Brás
E-mail: rjabras@hotmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Coexisting autoimmune diseases: an opportunity to associate immunobiologicals?

Coexistência de doenças autoimunes: oportunidade para a associação de imunobiológicos?

Isaac Teodoro Souza-e-Silva[1], Pablo Waldeck Gonçalves-de-Souza[1], Rossy Moreira Bastos-Junior[1], Sérgio Duarte Dortas-Junior[1], Solange Oliveira Rodrigues Valle[1]

ABSTRACT

Autoimmune diseases can be safely treated in clinical practice with immunobiologicals. The simultaneous occurrence of multiple immune-mediated diseases in the same individual could require a combination of immunobiologicals to control symptoms and improve quality of life. We report the case of a patient with rheumatoid arthritis who was receiving etanercept and required additional omalizumab for chronic spontaneous urticaria.

Keywords: Urticaria, angioedema, omalizumab, etanercept, biological therapy.

RESUMO

O tratamento das doenças autoimunes com imunobiológicos é uma opção segura na prática clínica. A simultaneidade na ocorrência de doenças imunomediadas em um mesmo indivíduo pode determinar a necessidade da associação dos imunobiológicos para controle dos sintomas e melhora da qualidade de vida dos doentes. Relatamos o caso de uma paciente com artrite reumatoide em uso de etanercepte, que necessitou da associação de omalizumabe para o tratamento de urticária crônica espontânea.

Descritores: Urticária, angioedema, omalizumabe, etanercepte, terapia biológica.

Introduction

Immunobiological therapy aims at optimize the therapeutic management for several diseases. It has changed the course of several immunoallergic diseases, such as urticaria, atopic dermatitis, and asthma, as well as a number of rheumatological and other diseases. Immunobiologicals have been the subject of several studies in recent years. Their efficiency in disease control has restored quality of life for patients suffering from severe and persistent symptoms. Thus, patients with associated comorbidities may benefit from the combined use of immunobiologicals in their therapeutic plan.

In this article, we report the case of a rheumatoid arthritis patient being treated with etanercept who required associated omalizumab for chronic spontaneous urticaria (CSU). The treatment was effective and safe.

Case report

A 66-year-old woman with rheumatoid arthritis had been using subcutaneous etanercept (anti-tumor necrosis factor) 50 mg weekly for 10 years. The disease was under control, with no new joint complaints and improved morning stiffness. She reported being treated for systemic arterial hypertension with losartan, having a thyroidectomy in 1977 (no cause was reported), and having recovered from hepatitis C in 2018.

1. Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ), Immunology Service - Rio de Janeiro, RJ, Brazil.

Submitted Apr 21 2023, accepted June 12 2023.

Arq Asma Alerg Imunol. 2023;7(2):209-12.

http://dx.doi.org/10.5935/2526-5393.20230027-en

In January 2020, she began having wheals associated with angioedema, mainly on the face and feet, with no specific trigger (Figure 1). She used oral corticosteroids for exacerbations, in addition to first-generation antihistamines prescribed by a dermatologist. After evaluation by an immunologist, following current guidelines for chronic urticaria, the following tests were performed - complete blood count, erythrocyte sedimentation rate, C-reactive protein, total IgE, and antithyroperoxidase tests were performed (Table 1). Although she was prescribed second-generation antihistamines (even quadruple doses), she had no success controlling the disease (urticaria control test [UCT] = 0 and urticaria activity score over 7 days [UAS7] = 42). In February 2022, she started using omalizumab 300 mg every 4 weeks and a quadruple dose of loratadine 10 mg/day. The disease was completely controlled (UCT = 16, UAS7 = 0) within 1 week of the first omalizumab dose. In September 2022, the interval between applications was increased, but after 4 weeks itching and urticaria returned (UCT = 11 and UAS7 = 10). Treatment was again prescribed at a 4-week interval, and the patient has remained on omalizumab 300 mg/4 weeks associated with loratadine 10 mg without showing further symptoms (UCT = 16 and UAS7 = 0). Table 2 shows the patient's laboratory results before and after beginning omalizumab in association with etanercept, which remained unchanged and within normal limits. Although both etanercept and omalizumab have been proven safe, since this patient had a history of methotrexate use for rheumatoid arthritis and previous hepatitis C virus infection, it was decided to monitor her metabolic panel as directed in the etanercept package insert.

Table 1
Laboratory tests performed between 02/24/2020 and 03/24/2021

Complete blood count:	
Hgb 14 g/dL	
Htc 42%	
Leukogram 10,100 mm^3 (0/0/0/0/0/0/66/29/5)	
Plt: 321,000	
AntiTPO < 5.0 UI/mL	IgE total 324 UI/mL
CRP 10 mg/dL	ESR 5 mm in 1 hour

Hgb = hemoglobin, Htc = hematocrit, Plt = platelets, AntiTPO = anti-thyroperoxidase, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate.

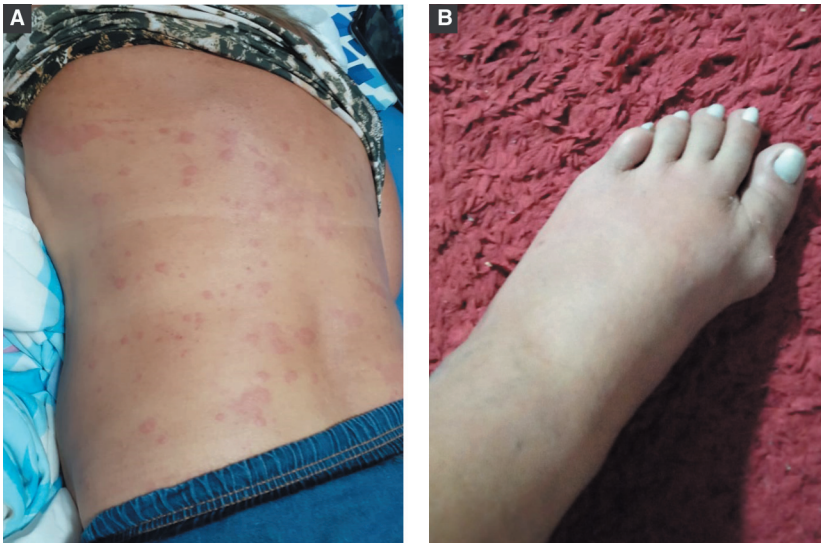

Figure 1
A) Patient's back with erythematous lesions due to chronic spontaneous urticaria.
B) Foot with erythematous lesions and hallux deformity characteristic of rheumatoid arthritis

Discussion

Urticaria is a debilitating disease that affects most patients entire bodies. CSU is characterized by episodes of urticaria and angioedema, or both, for > 6 weeks. Its pathophysiology is not fully understood, although tissue mast cell activation and inflammatory mediator release is the final common pathway of all forms of urticaria.[1] In addition to urticaria and angioedema, CSU is characterized by pruritus, which can be so intense that it incapacitates the patient.

Despite its low prevalence and complex etiology, in addition to its recurrent and unpredictable course, CSU can persist for years, with approximately 10% of patients presenting symptoms ≥ 5 years.[2] Women are more affected and the most affected age group is 20-40 years. Although its pathogenesis has not been fully elucidated, IgG-related autoimmunity and IgE-mediated autoallergy are the main mechanisms described in the literature.[3]

CSU is diagnosed through a detailed evaluation of the patient's clinical history and a physical examination to rule out other possible causes for the symptoms. No single specific diagnostic test has been developed.[4] Current guidelines recommend a complete blood count and erythrocyte sedimentation rate and/or C-reactive protein; specialists should order total and antithyroperoxidase IgE. The same guidelines recommend against extensive laboratory tests not guided by clinical history.[4]

CSU treatment is well established, aiming at complete symptom control so that patients can have a normal life.[4] The first line of treatment consists of monotherapy with daily doses of second-generation antihistamines; the dosage is dependent on the symptom, and can be even quadrupled to achieve complete control.[4]

In patients whose symptoms are refractory to quadruple monotherapy with second-generation antihistamines, association with omalizumab is indicated.[4] Omalizumab is a humanized anti-IgE monoclonal antibody that was initially used to treat severe allergic asthma. It selectively binds to circulating IgE, blocking its binding to mast cell and basophil receptors. Its effectiveness for CSU has been demonstrated in double-blind studies, as well as its safety for children > 12 years old, pregnant women, and patients with other diseases, such as cancer.[5]

It is indicated as an additional therapy for CSU (associated with second-generation antihistamines) in a subcutaneous dose of 300 mg every 4 weeks. The dose can be increased to 450 mg or 600 mg, and the time interval can be reduced to 2 weeks.

Etanercept blocks tumor necrosis factor, which is elevated in inflammatory diseases. It may be recommended for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis. It effectively reduces symptoms and is safe for long-term use, for example, to treat children > 2 years of age with juvenile idiopathic arthritis.[6]

CSU has been associated with autoimmune, atopic, and psychiatric diseases. In a meta-analysis of 60 studies, the prevalence of organ-specific autoimmune diseases in patients with CSU was 27.5%, among which autoimmune thyroid diseases stood out.[2] However, no studies have clearly linked these diseases with CSU.

Table 2
Laboratory tests pre- and post-treatment with omalizumab

Date	ALP	ALT	AST	GGT	Urea	Creatinine	Htc
Dec 2020	115 U/L	27 U/L	29 U/L	33 mg/dL	1.1 mg/dL	14.6 mg/dL	45.1%
Apr 2022	123 U/L	21 U/L	28 U/L	33 mg/dL	1.0 mg/dL	14.9 mg/dL	47%

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyl transferase, Htc = hematocrit.

These associations highlight the need to study omalizumab in combination with other immunobiologicals; there are few reports in the literature about the concomitant use of omalizumab and other biologics. A case was reported of a male patient who received guselkumab for psoriasis and omalizumab for CSU over a period of 21 months with no clinically relevant adverse effects or drug interactions.[7] In another case report, a patient developed CSU while using adalimumab for psoriatic arthritis. Omalizumab was prescribed concomitantly with adalimumab for 24 weeks, after which it was discontinued due to complete control of urticaria.[8] A recent study evaluated the combined use of omalizumab with other biologics (adalimumab, ustekinumab, secukinumab, and ixekizumab) indicated for psoriasis or hidradenitis suppurativa in 31 patients. No adverse events were observed due to the association, as has been found in other studies. One patient had diarrhea 9 months after adding omalizumab to secukinumab, which was resolved after discontinuing secukinumab.[3]

The greatest challenge to using a combination of immunobiologicals is the high cost of treatment. However, it is important consider whether these costs are outweighed by the natural course of some autoimmune diseases in the long term.

The present case described a patient with comorbidities and an extensive and complex pathological history who, after careful analysis, received a safe treatment that changed the course of her diseases without any side effects. Her laboratory results remained unchanged throughout treatment (Table 2), clearly demonstrating the safety of the combined treatment.

Therapeutic advances in chronic autoimmune diseases have prolonged the lives of patients. In patients with multiple diseases, combined immunobiologicals are becoming increasingly common. The safety of concomitant immunobiologicals, as seen in this case, is extremely important. The study of such combinations and the establishment of consensus and norms for their use is fundamental, as it can radically change the course of diseases and improve quality of life. This case report stands out for demonstrating the safety of a combination of immunobiologicals that act on different inflammatory response pathways to control debilitating and difficult-to-control chronic diseases.

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Abbreviations: RA = rheumatoid arthritis, anti-TPO = antithyroperoxidase, HCV = hepatitis C virus, CRP = C-reactive protein, UAS7 = urticaria activity score over 7 days, CSU = chronic spontaneous urticaria, UCT = urticaria control test, ESR = erythrocyte sedimentation rate.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Sérgio Duarte Dortas-Junior
E-mail: sdortasjr@gmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Omalizumab as urticaria treatment in the context of the COVID-19 pandemic

O omalizumabe no tratamento da urticária no contexto da pandemia de COVID-19

Luis Felipe Ensina[1], Sérgio Duarte Dortas-Junior[2], Rosana Câmara Agondi[3], Faradiba Sarquis Serpa[4], Solange Oliveira Rodrigues Valle[2], Roberta Fachini Jardim Criado[5], Joanemile Pacheco de-Figueiredo[6], Juliano Coelho Philippi[7], Fernanda Lugão Campinhos[4], Chayanne Andrade de-Araújo[1], Luisa Karla Arruda[8]

ABSTRACT

The beginning of the COVID-19 pandemic was marked by uncertainty due to lack of knowledge about the disease. Questions were raised about the use of immunobiologicals in the pandemic context, including omalizumab for patients with chronic urticaria (UC). This study assessed COVID-19 severity and the clinical course of urticaria in Brazilian patients on omalizumab therapy who were monitored by specialists. We retrospectively analyzed data from chronic urticaria patients treated with omalizumab between July, 2020 and June, 2021 who presented with COVID-19. Clinical characteristics and the course of urticaria during SARS-CoV2 infection were analyzed. The sample consisted of 28 patients treated with omalizumab, 27 of whom had chronic spontaneous urticaria (UCE) and 25% of whom had associated chronic inducible urticaria. Most of the patients (71%) were using quadruple doses of second-generation antihistamines associated with omalizumab. The symptoms of all patients were controlled. The most frequent symptoms during COVID-19 were: fever (43%), headache (36%), malaise (32%), hypo/anosmia (29%) and cough (21%). Four patients were hospitalized, including 1 in intensive care. One patient reported worsening chronic urticaria

RESUMO

O início da pandemia de COVID-19 foi marcado por incertezas diante do desconhecimento sobre a doença. Uma série de dúvidas relacionadas ao uso de imunobiológicos no contexto da pandemia foi levantada, inclusive em relação ao tratamento com omalizumabe em pacientes com urticária crônica (UC). Este estudo teve como objetivo analisar os dados relacionados à gravidade da COVID-19 e a evolução da urticária em pacientes em terapia com omalizumabe acompanhados por especialistas no Brasil. Foi realizada análise retrospectiva de dados de pacientes com UC tratados com omalizumabe entre julho/2020 e junho/2021 que apresentaram COVID-19. Foram avaliados dados relacionados às características clínicas dos pacientes e evolução da urticária durante a infecção pelo SARS-CoV2. Foram incluídos 28 pacientes em tratamento com omalizumabe, sendo 27 com urticária crônica espontânea (UCE), dos quais 25% tinham alguma urticária induzida associada. A maior parte dos pacientes (71%) estavam utilizando doses quadruplicadas de anti-histamínicos modernos de 2ª geração associados ao omalizumabe. Todos os pacientes estavam com os sintomas controlados. Entre os sintomas apresentados durante a COVID-19, os mais frequentes foram: febre (43%), ce-

1. Universidade Federal de São Paulo - São Paulo, SP, Brazil.
2. Universidade Federal do Rio de Janeiro - Rio de Janeiro, RJ, Brazil.
3. Universidade de São Paulo, Department of Allergy & Clinical Immunology - São Paulo, SP, Brazil.
4. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - Vitória, ES, Brazil.
5. Faculdade de Medicina do ABC - Santo André, SP, Brazil.
6. Universidade Federal da Bahia - Salvador, BA, Brazil.
7. Private Practice - Cuiabá, MT, Brazil.
8. Ribeirão Preto School of Medicine - Universidade de São Paulo - Ribeirão Preto, SP, Brazil.

Submitted Mar 20 2023, accepted Apr 18 2023.

Arq Asma Alerg Imunol. 2023;7(2):213-8.

http://dx.doi.org/10.5935/2526-5393.20230028-en

symptoms while infected with COVID-19. Five (18%) patients experienced worsening chronic urticaria symptoms after recovery from COVID-19. All patients recovered from COVID-19 without serious sequelae. Omalizumab did not appear to increase the risk of severe COVID-19 and can be safely used in patients with chronic urticaria.

Keywords: Urticaria, omalizumab, COVID-19.

faleia (36%), mal-estar (32%), hipo/anosmia (29%) e tosse (21%). Quatro pacientes foram hospitalizados, um deles em unidade de terapia intensiva. Um paciente relatou piora dos sintomas da UC durante a COVID-19. Cinco (18%) pacientes apresentaram piora dos sintomas da UC após a resolução da COVID-19. Todos os pacientes se recuperaram da COVID-19 sem sequelas graves. O OMA não pareceu aumentar o risco de COVID-19 grave e poderia ser usado com segurança em pacientes com UC.

Descritores: Urticária, omalizumab, COVID-19.

COVID-19, the disease caused by SARS-CoV-2 coronavirus, was first described in 2019. Its main manifestations were fever, flu-like symptoms, pneumonia, severe acute respiratory syndrome, diarrhea, and hyposmia, indicating its systemic nature.[1] On March 11, 2020, the World Health Organization declared COVID-19 a pandemic.[2] At that point, when both the virus and the disease were still little known and the number of deaths was progressively increasing, questions were raised about populations at greater risk for serious illness, such as immunosuppressed patients and those with chronic pathologies and severe comorbidities.[3] Among immunologists, one of the most pressing questions was whether immunobiologicals would affect the course of COVID-19, putting patients undergoing immunobiological treatment at greater risk for more severe COVID-19.[4]

Chronic urticaria (CU) significantly impacts the quality of life of poorly controlled patients. About 40% of cases do not respond to antihistamines and are indicated for omalizumab (OMA), an anti-IgE antibody considered the first treatment option for these patients.[5,6]

It has been demonstrated that OMA treatment can restore interferon-alpha-mediated response to both rhinovirus and influenza by reducing expression of high-affinity IgE receptors on the surface of cells, including mast cells, basophils, and plasmacytoid dendritic cells, which suggests that OMA has an antiviral role.[7-9] Thus, theoretically, OMA treatment should not be suspended in patients with mild to moderate COVID-19. However, at the beginning of the pandemic, most experts recommended that in patients with severe COVID-19, OMA should be suspended until at least 2 weeks after recovery.[4]

Due to the limited information and uncertainty about OMA use during acute SARS-CoV-2 infection, we analyzed data on COVID-19 severity and the course of urticaria in patients followed by specialists in Brazil.

Methods

This retrospective study analyzed the medical records of CU patients undergoing OMA treatment who had a confirmed or highly suspected SARS-CoV-2 infection between July 2020 and June 2021. Infections were considered confirmed after positive COVID-19 test results (RT-PCR, rapid immunodiagnostic test, and IgM and/or IgG serology) or highly suspected when there was a strongly suggestive epidemiological history associated with flu-like symptoms.

The following data were collected from the medical records of each patient: sex, age, CU subtype, time since CU onset, urticaria treatment at the time of SARS-CoV-2 infection, COVID-19 symptoms, hospitalization for COVID-19, the use of nonsteroidal anti-inflammatory drugs, and the course of urticaria after COVID-19.

Patient and SARS-CoV-2 infection data are described below.

Results

We included 28 patients undergoing OMA treatment (79% female) who were diagnosed with COVID-19 according to the above-mentioned criteria. The mean patient age was 38.5 (SD, 10) years. Almost all patients had been diagnosed with CSU. Among these, seven (25%) had some associated

chronic inducible urticaria: dermographism (3), solar urticaria (3), or delayed pressure urticaria (1). Only 1 patient had isolated chronic inducible urticaria (solar urticaria). The mean duration of urticaria was 7.6 (range, 1.3-26) years. Most patients (71%) were using a quadruple dose of modern second generation antihistamines associated with OMA, and 8 patients (29%) were on OMA monotherapy. The symptoms of all patients were controlled (urticaria control test score ≥ 12 or urticaria activity score over 7 days ≤ 6) prior to SARS-CoV-2 infection.

COVID-19 diagnosis was confirmed by RT-PCR in 18 patients; 4 (14%) had positive IgM and/or IgG serology for SARS-CoV-2; 3 (11%) had positive results in a rapid immunodiagnostic test for SARS-CoV-2. Three presented highly suggestive symptoms after contact with COVID-19 patients during the pandemic. The most frequently observed symptoms were fever (43%), headache (36%), malaise (32%), hyposmia/anosmia (29%), cough (21%), dyspnea (11%), and dysgeusia (7%). Four patients were hospitalized, one in the intensive care unit. Seven patients were treated with nonsteroidal anti-inflammatory drugs, which had no direct impact on urticaria control. One patient reported worsening CU symptoms while infected. Five (18%) experienced worsening CU symptoms after recovering from COVID-19 (Table 1). All patients recovered from COVID-19 without serious sequelae.

Discussion

CU treatment aims at complete symptom control, and OMA therapy can control the disease in up to 85% of patients.[6,10] Viral infections are a frequent cause of acute urticaria and can be an exacerbating factor in chronic urticaria.[11] SARS-CoV-2 infection has also been associated with manifestations of acute urticaria, with an incidence between 1.9% and 3.4%.[1,12] A Turkish study found no significant association between positive RT-PCR for SARS-CoV-2 and treatment type (antihistamines, OMA, or both) in a subgroup of 15 patients with CSU who presented COVID-19-related symptoms, suggesting that OMA treatment does not predispose to or prevent SARS-CoV-2 infection.[13]

Our data suggest that patients whose symptoms have been controlled through OMA have a low risk of exacerbated CSU during SARS-CoV-2 infection. However, most studies have shown that urticaria appears after COVID-19 symptom onset.[1] Interestingly, 5 patients reported worsening symptoms after recovering from COVID-19, even though their urticaria treatment remained unchanged. Mutean et al. reported that 44% of patients with CSU and COVID-19 experience worsening urticaria during infection, especially those with moderate to severe COVID-19.[14] Passante et al. observed no CSU exacerbation in their series of 7 patients who were being treated with OMA and tested positive for COVID-19 but had mild or no symptoms.[15] OMA controls urticaria symptoms by reducing mast cell activation and releasing mast cell mediators. It is possible that the antiviral effects of OMA could dampen infection and inflammation in mild cases of COVID-19, preventing urticaria from worsening. However, OMA may be insufficient to overcome the effects of more severe infection, which can trigger or worsen urticaria symptoms.

Our data also suggest that OMA treatment does not increase the risk of severe COVID-19. However, 4 of the patients who tested positive for COVID-19 were hospitalized, indicating moderate to severe illness. A retrospective analysis of patients from Romania with CSU found that 71% of patients with CSU and SARS-CoV-2 infection had moderate to severe COVID-19, but that treatment with OMA was not associated with COVID-19 severity.[14] Kocatürk et al. reported that 90% of patients with COVID-19 who were being treated with OMA +/- antihistamines had mild COVID-19, and only 2 patients required hospitalization.[16] Ayhan et al. reported on 3 CSU patients treated with OMA who had mild COVID-19.[17] Paulino et al. also reported on a CSU patient treated with OMA whose only symptoms during SARS-CoV-2 infection were anosmia and arthralgia.[18] Overall, current data suggest that OMA treatment in patients with CU is not a risk factor for more severe COVID-19.

In conclusion, our results suggest that most patients can continue OMA therapy despite SARS-CoV-2 infection. OMA did not appear to increase the risk of severe COVID-19 and could be safely used in patients with CU. However, further studies are needed with larger patient samples to more conclusively recommend continued use of OMA in CU patients with COVID-19.

Table 1
Clinical characteristics of the patients

Patient ID	Sex	Age (y)	CU subtypes	COVID test results	CU treatment (besides OMA)	Months from CU onset to COVID-19	Months since beginning OMA treatment	Hospitalized for COVID-19
1	M	33	CSU	SARS-CoV2 rapid immunodiagnostic test	Second generation anti-H1 (4X)	204	16	No
2	F	47	CSU, delayed pressure urticaria	IgM serology and/or IgG SARS-CoV2	Second generation anti-H1 (2X)	114	24	No
3	F	43	CSU	RT-PCR	None	60	48	No
4	F	36	CSU	RT-PCR	None	72	68	No
5	F	41	CSU	RT-PCR	Second generation anti-H1 (4X)	24	Unknown	No
6	F	57	CSU, dermographism	IgM serology and/or IgG SARS-CoV2	Second generation anti-H1 (on demand)	36	26	No
7	M	46	CSU, dermographism	RT-PCR	Second generation anti-H1 (on demand)	60	25	No
8	F	43	CSU	RT-PCR	None	60	Unknown	No
9	F	33	CSU	RT-PCR	Second generation anti-H1 (4X)	48	33	No
10	F	40	CSU, solar urticaria	High clinical suspicion	Second generation anti-H1 (2X)	240	7	Yes
11	F	56	CSU	RT-PCR	Second generation anti-H1 (2X)	154	8	No
12	F	50	CSU	IgM serology and/or IgG SARS-CoV2	Second generation anti-H1 (licensed dose)	72	60	No
13	M	31	CSU	RT-PCR	Second generation anti-H1 (2X)	60	12	No

CU = chronic urticaria, CSU = chronic spontaneous urticaria, OMA = omalizumab, RT-PCR = reverse transcriptase-polymerase chain reaction.

Table 1 *(continuation)*
Clinical characteristics of the patients

Patient ID	Sex	Age (y)	CU subtypes	COVID test results	CU treatment (besides OMA)	Months from CU onset to COVID-19	Months since beginning OMA treatment	Hospitalized for COVID-19
14	F	12	CSU	RT-PCR	Second generation anti-H1 (licensed dose)	15	11	No
15	F	22	Solar urticaria	RT-PCR	None	36	20	No
16	F	47	CSU	IgM serology and/or IgG SARS-CoV2	Second generation anti-H1 (licensed dose)	114	24	No
17	F	34	CSU	RT-PCR	Second generation anti-H1 (licensed dose)	84	24	No
18	F	37	CSU	RT-PCR	Second generation anti-H1 (4X)	16	0.5	No
19	M	38	CSU	RT-PCR	Second generation anti-H1 (licensed dose)	18	9	No
20	F	44	CSU	SARS-CoV2 rapid immunodiagnosis test	Second generation anti-H1 (4X)	312	28	No
21	M	47	CSU	RT-PCR	None	36	20	No
22	F	38	CSU	SARS-CoV2 rapid immunodiagnosis test	Second generation anti-H1 (4X)	41	5	No
23	F	33	CSU, dermographism	RT-PCR	Second generation anti-H1 (licensed dose)	144	50	No
24	F	38	CSU	RT-PCR	None	41	5	No
25	M	19	CSU	RT-PCR	Second generation anti-H1 (2X)	70	62	No

CU = chronic urticaria, CSU = chronic spontaneous urticaria, OMA = omalizumab, RT-PCR = reverse transcriptase-polymerase chain reaction.

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Conflict of interests: L.F. Ensina has received speaker fees from Novartis, Sanofi, and Abbvie; support to attend Novartis and Sanofi scientific meetings; and participates in clinical research with Novartis, Sanofi and Amgen. S. Dortas Jr. has received speaker fees from AstraZeneca, Chiesi and Novarti; and support to attend Sanofi, Takeda, and CSL Behring scientific meetings. F.S. Serpa has received speaker fees from Novartis, Takeda, and GSK; and support to attend Takeda and GSK scientific meetings. S.O.R. Valle has received speaker fees from Novartis, Takeda, CSL Behring and AstraZeneca; consultancy from Takeda, CSL Behring and Novartis; and support to participate in Takeda and CSL Behring scientific meetings. R.F.J. Criado has received speaker fees from Novartis, Mantecorp, and Sanofi; consultancy for Sanofi, Abbvie and Novartis; and support to attend Sanofi and Takeda scientific meetings. L.K. Arruda has received speaker fees from Novartis, Sanofi, GSK, AstraZeneca and Takeda. R.C. Agondi, J.P. Figueiredo, J.C. Philippi, F.L. Campinhos e C.A. de Araújo declare no conflicts of interest.

Corresponding author:
Luis Felipe Ensina
E-mail: 100alergia@gmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Anaphylaxis and systemic mastocytosis caused by *Solenopsis invicta* stings

Anafilaxia e mastocitose sistêmica ocasionada pela Solenopsis invicta

Mario Geller[1], Phillip Scheinberg[2], Mariana C. Castells[3]

ABSTRACT

Indolent systemic mastocytosis is a rare disease characterized by an increased number of mast cells in the bone marrow and other tissues, such as the liver, spleen, lymph nodes, and skin. Patients with indolent systemic mastocytosis and high serum tryptase levels are at risk for Hymenoptera venom-induced anaphylaxis. Hymenoptera venom immunotherapy in patients with specific IgE is safe and effective. While some patients can receive ultra-rush venom immunotherapy with minimal side effects, omalizumab effectively protects against anaphylaxis during the build-up phase.

Keywords: Anaphylaxis, indolent systemic mastocytosis, urticaria pigmentosa, imported fire ant, *Solenopsis invicta*, hymenoptera venom immunotherapy, hereditary alpha-tryptasemia.

RESUMO

A mastocitose sistêmica indolente é uma doença rara caracterizada por um número aumentado de mastócitos na medula óssea e em outros tecidos, como fígado, baço, linfonodos e pele. Pacientes com mastocitose sistêmica indolente e altos níveis séricos de triptase correm risco de anafilaxia induzida pelo veneno dos *Hymenoptera*. A imunoterapia com veneno de himenópteros em pacientes com IgE específica é segura e eficaz. Embora alguns pacientes possam receber imunoterapia com veneno ultrarrápido com efeitos colaterais mínimos, o omalizumabe protegeu efetivamente contra a anafilaxia durante a fase de acúmulo.

Descritores: Anafilaxia, mastocitose sistêmica indolente, urticária pigmentosa, formiga-de-fogo importada, *Solenopsis invicta*, imunoterapia com veneno de himenópteros, alfa triptasemia hereditária.

Indolent systemic mastocytosis (ISM) is a rare disease characterized by an increased number of mast cells (MCs) in the bone marrow (BM) and other tissues, such as the liver, spleen, lymph nodes, and skin, and a normal life span. Skin lesions associated with ISM are typically maculo papular monomorphic lesions, also known as urticaria pigmentosa (UP). When UP lesions are stroked, a wheal and flare reaction is noted within a few minutes, known as Darier's sign.[1-3] Patients with ISM and high serum tryptase levels are at risk for Hymenoptera venom-induced anaphylaxis, which is more common in males. These patients with Hymenoptera venom-specific IgE are candidates for immunotherapy, which is recommended for life, and is effective at protecting most patients from future severe anaphylactic episodes.[4,5] We present here the first case of life-threatening anaphylaxis following multiple stings from imported fire ants (IFA) in a female as the presenting symptoms leading to the diagnosis of ISM.[6]

1. Division of Medicine, Academy of Medicine of Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
2. Division of Hematology, Hospital A Beneficência Portuguesa, São Paulo, SP, Brazil.
3. Mastocytosis Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

Submitted: Oct 20 2022, accepted: Nov 28 2022.

Arq Asma Alerg Imunol. 2023;7(2):219-21.

http://dx.doi.org/10.5935/2526-5393.20230029-en

Case report

A 31-year-old caucasian woman presented with a long history of perennial allergic rhinitis and atopic dermatitis as a child. While outdoors and barefoot, she was stung for the first time by multiple IFA in her legs and feet. She immediately developed throat tightening with difficulty breathing, and abdominal cramping pains, became hypotensive, and developed grand mal seizures with fecal and urine incontinence. She was resuscitated with three IM 0.3mg epinephrin injections, promethazine 50mg IV (H1-antihistamine), hydrocortisone 300mg IV, replacement fluids, and oxygen, recovering within a few hours without sequelae. She tested positive in prick skin testing and serum-specific IgE to IFA *Solenopsis invicta* (Si) (0.47 kU/L; negative value below 0.10 kU/L), house dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, and *Blomia tropicalis*), dogs, cats, and horses. Blood cell counts, platelets, liver, and renal function tests were all normal. Specific IgE to honey bee, wasp and hornets were all negative.

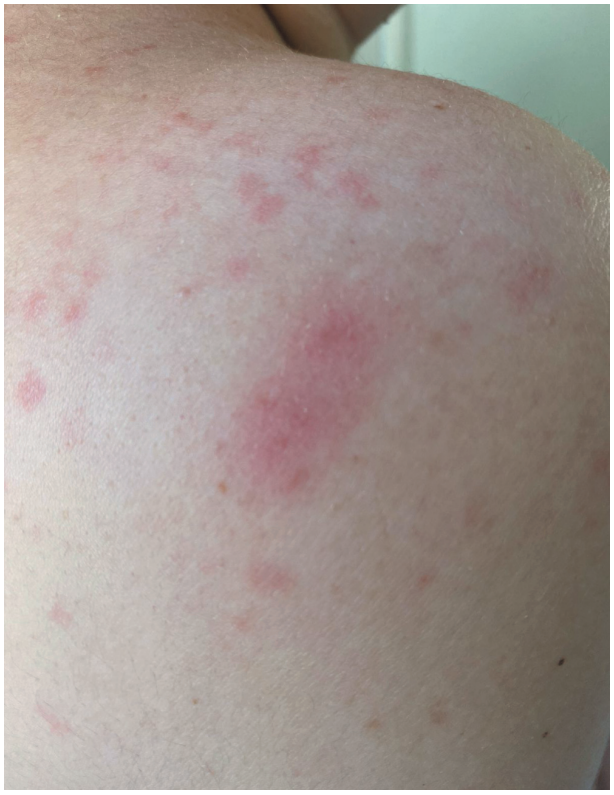

Figure 1
Positive Darier's sign after stroking the urticaria pigmentosa lesions

Serum tryptase levels were 22.8 and 23.7 ng/mL at baseline (normal value below 11.4 ng/mL). Peripheral blood KIT mutations in exons 8 and 17 were not detected. A bone marrow biopsy was obtained and showed a negative KIT D816V mutation. The histology presented aggregates of 15 or more MCs stained by tryptase, CD117 spindle-shaped forms, and aberrant expression of CD25, negative for CD2, CD3, CD30, and CD34. An abdominal CT scan was negative for hepatosplenomegaly, and a DEXA scan showed osteopenia. The diagnosis of ISM was established. The patient developed photo-allergic dermatitis to a solar protection cream containing parabens with a generalized flare of UP lesions with a positive Darier's sign (Figure 1). Genetic testing showed a normal alpha-tryptase copy number 1 for the gene TPSAB1 (GENEbyGENE, Houston, TX), ruling out Hereditary alpha tryptasemia (HαT). Her medications included: 20mg H1-antihistamine bilastine, 400mg H2-antihistamine cimetidine,10mg montelukast, calcium, and vitamin D. Fluticasone furoate nasal spray was prescribed for allergic rhinitis. During acute episodes of UP flares, the patient uses 40mg prednisolone and topical 0.1% tacrolimus ointment. She carries three 0.3mg epinephrine autoinjectors all the time The patient was treated with immunotherapy with IFA-whole body extract, and has achieved monthly maintenance dosing with 0.5mL of 1:100 wt/vol Si (Greer, Lenoir, North Carolina). No more episodes of anaphylaxis have occurred for over a year.

Discussion

This case illustrates the need to obtain baseline serum tryptase measurement in all patients with Hymenoptera venom anaphylaxis to screen for mast cell activation disorders.[6] A value above the normal range should prompt the determination of KIT D816V mutation in peripheral blood and a bone marrow biopsy. Severe anaphylaxis has also been associated with HαT, with duplication of TPSAB1 alpha-tryptase gene. In this case the TPSAB1 copy number analysis was normal, ruling out HαT. Hymenoptera venom immunotherapy in patients with specific IgE is safe and effective.[7] While some patients can receive ultrarush venom immunotherapy with minimal side effects, omalizumab has effectively protected against anaphylaxis during the build-up phase.[8]

Acknowledgment

To Salmo Raskin, MD, PhD for genetic assistance.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Mario Geller
E-mail: drmariogeller@gmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Anaphylaxis associated with intracavernous penile injection of prostaglandin E1 in combination with papaverine and phentolamine

Anafilaxia associada à injeção intracavernosa peniana de prostaglandina E1 em combinação com papaverina e fentolamina

Mario Geller[1]

ABSTRACT

Total radical prostatectomy for advanced prostate cancer may lead to sexual impotence, since it is associated with severe erectile dysfunction. A widely recommended treatment for this disabling condition is intracavernous penile injection of a mixture of prostaglandin E1, papaverine, and phentolamine. To our knowledge, we present the first case of anaphylaxis associated with intracavernous penile injection of prostaglandin E1 in combination with papaverine and phentolamine.

Keywords: Anaphylaxis, papaverine, phentolamine, prostaglandin E1, adverse effects, treatment with combination drugs.

RESUMO

A prostatectomia radical total para câncer de próstata avançado pode levar à impotência sexual, associada a uma disfunção erétil grave. Um tratamento amplamente recomendado para esta condição incapacitante é a injeção intracavernosa no pênis de uma mistura de prostaglandina E1, papaverina e fentolamina. Até onde sabemos, estamos apresentando o primeiro caso de anafilaxia associada à injeção intracavernosa peniana de prostaglandina E1 em combinação com papaverina e fentolamina.

Descritores: Anafilaxia, papaverina, fentolamina, prostaglandina E1, efeitos adversos, tratamento com medicamentos combinados.

Total radical prostatectomy for advanced prostate cancer may lead to sexual impotence, associated with a severe erectile dysfunction. A widely recommended treatment for this disabling condition is the penis intracavernous injection of a mixture of prostaglandin E1, papaverine, and phentolamine. This combination results in a significantly increased degree of erection.[1,2] We report the case of a patient with recurrent episodes of severe anaphylaxis following this treatment, used prior to intercourse.

A 62-year-old White man underwent radical prostatectomy for advanced prostate cancer 9 years ago. Since then, he has been managing sexual impotence, with severe erectile dysfunction, by administering a penis intracavernous injection of a mixture containing prostaglandin E1, papaverine, and phentolamine prior to intercourse. Over the past 3 months, he experienced 3 anaphylactic episodes minutes after intercourse, in all of which the usual multidrug intracavernous injection had been administered. In all 3 events, he experienced general flushing, extensive itching, paresthesia, dyspnea, and dizziness with hypotension (measured blood pressure 70 x 40 mm Hg). There was no laryngeal edema,

1. Geller Allergy and Immunology Clinic, Rio de Janeiro, RJ, Brazil.

Submitted: Oct 20 2022, accepted: Nov 28 2022.

Arq Asma Alerg Imunol. 2023;7(2):222-4.

http://dx.doi.org/10.5935/2526-5393.20230030-en

urticaria, or angioedema. The symptoms subsided about 15 minutes after taking fexofenadine 180 mg orally. The injection mixture contains prostaglandin E1 20 µg/mL, papaverine 12 mg/mL, and phentolamine 3.3 mg/mL. Allergy skin testing with the injection mixture, using positive and negative controls, showed positive reactions to the prick (3 mm wheal) and intradermal (12 mm wheal) tests (Figure 1). A persistent delayed positive reaction at the intradermal site was documented 24 hours later (Figure 2). Blood cell counts, platelets, liver and renal function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complements (C3, C4, CH50-100), serum immunoglobulins IgG, IgA, IgM, and IgE (66.60 IU/mL), serum tryptase (5.98 ng/mL), and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) were all normal.

The patient clearly presented 3 severe episodes of anaphylaxis following the administration of the multidrug injection into the cavernous region of the penis. Any of the substances in the mixture could be the trigger, although prostaglandin E1 and papaverine are the most likely triggers. An IgE-mediated reaction is a possibility. This mixture has been shown to cause anaphylactic histamine release from rat mast cells.[3,4] We have recommended that the patient should carry a 0.3-mg epinephrine auto-injector and further discuss with the urologist the possibility of using a penile prosthetic device prior to intercourse.

To our knowledge we are presenting the first case of anaphylaxis associated with penis intracavernous injection of prostaglandin E1 in combination with papaverine and phentolamine.

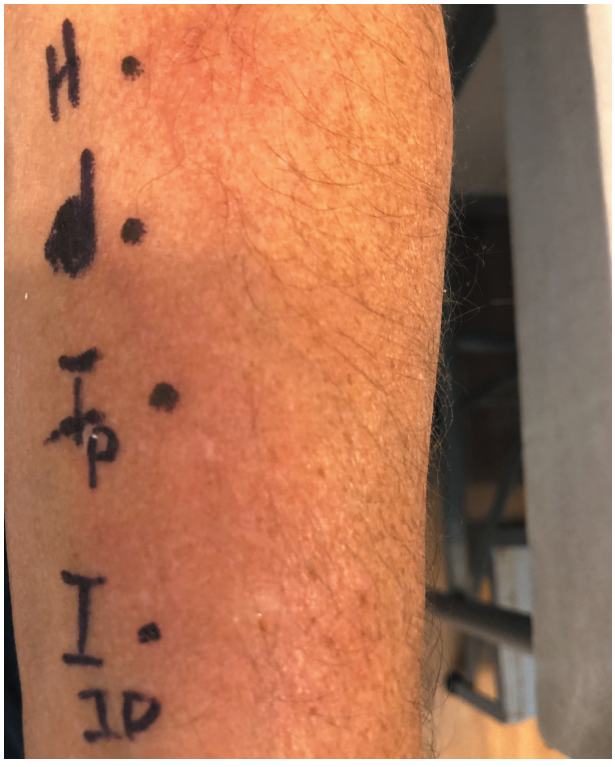

Figure 1
Positive immediate allergy skin tests with the patient's injection mixture

H – Histamine positive control.
d – Diluent negative control.
I P – Skin prick test positive to the injection mixture.
I ID – Intradermal skin test positive to the injection mixture.

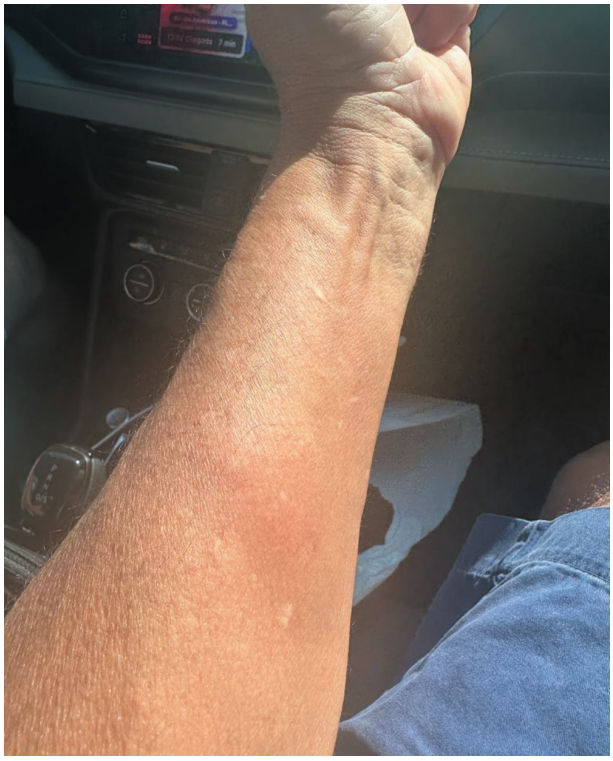

Figure 2
Delayed 24-hour positive allergy skin test with the patient's injection mixture

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Mario Geller
E-mail: drmariogeller@gmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Desensitization immunotherapy for *Malassezia spp.*: experimental case report

Imunoterapia de dessensibilização para Malassezia *spp.: relato de caso experimental*

Raphael Coelho Figueiredo[1], Caroline Braga Barroso[2], Livio Melo Barbosa[2], Márcia Gabrielly Teles de-Macedo[2], Peniel Leite Rocha[2], Andréa Maria de Araújo Mendes[2], Lara Milena Santos Silva[3], Elaine de Lima de-Almeida[1]

ABSTRACT

Pityriasis versicolor is a infection caused by *Malassezia* yeast species, which, despite simple management, involves a high risk of recurrence and chronicity, and there are few effective therapies for resistant strains. Desensitization for *Malassezia spp.* has been reported in the literature, but for atopic dermatitis, rather than pityriasis versicolor, making this an innovative report. The case presented herein is of a 28-year-old man who had typical manifestations of pityriasis versicolor in the face, cervical, dorsal, and axillary region for 4 years that were resistant to topical and systemic therapies. Once the ineffectiveness of traditional therapies had been determined, weekly *Malassezia* desensitization sessions were begun, progressively increasing first in dosage and then in frequency. After 11 months, the lesions had improved completely. In this case, immunotherapeutic techniques effectively treated pityriasis versicolor, although the evidence is as yet insufficient to support large-scale use.

Keywords: *Malassezia*, tinea versicolor, desensitization, immunological, case reports.

RESUMO

A pitiríase versicolor (PV) consiste em uma infecção fúngica ocasionada por leveduras de *Malassezia spp.*, que apesar de manejo simples, é uma doença com elevadas chances de recidiva e cronificação, além da pouca variedade de terapias efetivas para tratar cepas resistentes. Existem relatos na literatura sobre utilização de dessensibilização para *Malassezia spp.*, mas para o tratamento de dermatite atópica e não PV, conferindo caráter inovador ao relato em questão. O caso apresentado consiste em um paciente de 28 anos, do sexo masculino, com manifestações típicas de PV em região de face, cervical, dorsal e axilar, há 4 anos, com resistência aos esquemas terapêuticos tópicos e sistêmicos. Uma vez identificada a ineficácia das terapias tradicionais, foi iniciado o tratamento com dessensiblização para *Malassezia spp.*, em aplicações semanais, com aumento progressivo da dosagem e posterior aumento no intervalo das aplicações. Após onze meses de realização do novo tratamento, o paciente evoluiu com melhora completa das lesões. Conclui-se que a utilização de técnicas imunoterápicas para o tratamento de PV foi considerado eficaz no caso relatado, apesar de ainda não haver evidências que amparem sua utilização em maior escala.

Descritores: *Malassezia*, tinha versicolor, dessensibilização imunológica, relatos de casos.

1. Clinic of Allergy and Clinical Immunology (CAAIC) - Imperatriz, MA, Brazil.
2. Universidade Federal do Maranhão, School of Medicine – Imperatriz Science Center - Imperatriz, MA, Brazil.
3. Universidade Estadual da Região Tocantina do Maranhão – School of Medicine - UEMASUL - Imperatriz, MA, Brazil.

Submitted Sept 27 2022, accepted Apr 19 2023.

Arq Asma Alerg Imunol. 2023;7(2):225-30.

http://dx.doi.org/10.5935/2526-5393.20230031-en

Introduction

Pityriasis versicolor (PV), also known as tinea versicolor, is a common, superficial, and benign fungal infection caused by yeasts belonging to the genus *Malassezia* (formerly *Pityrosporum*). Fourteen species of *Malassezia* have been described so far; those mainly associated with to PV are *M. furfur*, *M. globosa*, and *M. sympodialis*.[1]

These pseudo-yeasts are dimorphic, saprophytic, lipid-dependent fungi found in the normal flora of the skin. However, due to the influence of endogenous and exogenous factors, such as hyperhidrosis, the use of topical oils, immunosuppression, endocrine disorder, malnutrition, genetic predisposition, etc., these fungi convert to a pathogenic mycelial form associated with the onset of typical clinical manifestations of PV.[2] The infection most commonly affects adolescents and young adults, since, due to increased androgenic stimuli in these stages of life, the sebaceous glands reach peak functioning, predisposing this population to fungal colonization.[3,4]

This dermatosis is marked by lesions that can manifest as spots or fine scaly plaques with variable changes in skin pigmentation, including hypopigmented, hyperpigmented and/or slightly erythematous regions. The neck, trunk, and proximal extremities are the most commonly affected sites, with the intertriginous areas and face being less common.[5] The change in skin color is the patient's main complaint, mainly because it involves social stigma.[6]

Topical antifungals are the first-line treatment for PV, with oral imidazoles or terbinafine used for more extensive manifestations.[7] However, despite being easy to treat in clinical practice, PV's recurrence rate is high – up to 80% within 2 years.[1,7] Thus, recurrence after treatment with adequate antifungal agents and "chronification" are major complaints.[8]

Therefore, new therapies should be considered, since few classes of antifungals are available and infections by resistant strains are increasing.[9] Alternative therapeutic protocols, such as subcutaneous immunotherapy for *Malassezia* desensitization or the administration of yeast adhesion factor inhibitors have been reported, although the literature on the subject is still limited.[10]

Desensitization immunotherapy was developed more than a century ago to stimulate the immune system of allergic patients, modulating their response to allergens and creating a kind of immunological tolerance.[11] To accomplish this, doses of the same allergen are introduced in gradually larger amounts, functioning as a specific therapeutic vaccine.[12]

To reduce the reactivity of allergen extracts, allergoids, molecules polymerized through chemical agents, such as glutaraldehyde or formaldehyde, or biological agents, such as transglutaminase, can be produced. Thus, desensitization immunotherapy is expected to interrupt and modify the natural course of the disease.[12]

With this in mind, the present study reports a case of recurrent PV treated with desensitization immunotherapy for *Malassezia* spp., a little-discussed antifungal therapy with innovative potential.

Case report

A male 28-year-old market analyst born in Imperatriz, Maranhão (northeastern Brazil) sought out our allergology service due to hypopigmented spots in the cervical region, the back, and the face, and hyperpigmented and erythematous spots in the axillary region for 4 years (Figure 1), including clinical improvement and subsequent recurrence after topical and oral antifungal therapy.

Lesion biopsy revealed mild acanthosis of the epidermis and focal vacuolar alteration of the basal layer, in addition to slight mononuclear infiltrate, confirming the diagnosis of superficial perivascular dermatitis. Traditional laboratory analysis, including direct mycological examination and culture with antifungigram, showed mycosis by *Malassezia* spp. resistant to several oral and topical antifungals, which indicated PV. The case was then forwarded to a professional dermatologist. During dermatological care, the patient still had erythematous papules in the cervical and both infra-axillary regions, with positive results for Zileri's sign, well-defined hyperpigmented macules in the groin, and onychomycosis in the nails. At that point, treatment consisted of oral terbinafine, topical isoconazole and fenticonazole, as well as a hydroalcoholic solution with 2.5% selenium sulfide. Although the lesions were monitored monthly, adjusting the medication as necessary, the patient still had active PV lesions in the cervical region and scaly lesions in both axillary regions.

The patient was followed up for 1 year by an allergist and 4 months by a dermatologist, which, in addition to the previous 4-year history of lesions, totaled 5 years and 4 months living with active PV,

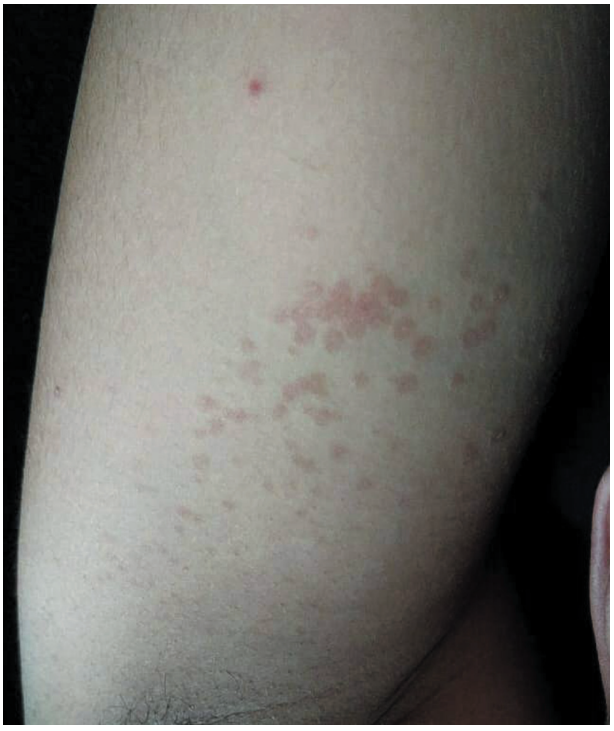

Figure 1
Stain-like lesions and erythematous papules in the right infra-axillary region

including recurrences and unsatisfactory therapeutic results. The patient was thus sent back to the allergist to assess the benefits of desensitization.

The possibility of atopic dermatitis was ruled out due to the characteristics, location, and evolution of the lesions. Contact dermatitis was also excluded after a negative result in the patch test (the Brazilian standard battery; IPI ASAC Brasil®). A laboratory investigation was performed for immunodeficiencies, and the patient was negative for inborn errors of immunity.

Scrapings from the lesion were collected in the laboratory. To avoid other pathogens in the sample, the scraped surface was first disinfected with iodine solution (1% to 2% iodine tincture), which was removed with 70% alcohol and then left to dry prior to collection. After culture, 2 µg *Malassezia* spp. was isolated in 0.9% saline for a prick test to assess the patient's specific IgE response in a healthy control. The patient was positive for *Malassezia* spp. at 10 mm, with a positive control at 7 mm and negative control at 2 mm; the healthy control was negative for *Malassezia* spp.

In early April 2019, all pharmacological treatment was suspended and specific immunotherapy for *Malassezia* spp. began. The protocol differed in the number of applications, intervals, and dilution patterns from that used in allergen-specific immunotherapy for patients sensitized to house dust mites. The experimental treatment was approved by the Human Research Ethics Committee of the Federal University of Maranhão's University Hospital (opinion 5,375,840). The patient provided written informed consent for both the treatment and publication of the results. All data remained confidential and were anonymized under the responsibility of the researchers, in accordance with National Health Council Resolution 466/2012.

A slower (more gradual) desensitization protocol was planned, since this therapy was experimental and involved the risk of systemic reactions. The allergen was diluted in an aqueous solution of phenol + 0.9% physiological saline solution (IPI ASAC Brasil®). The weekly application began with 4 injections per visit, with progressively increasing doses: 0.1 mL, 0.2 mL, 0.4 mL, and 0.8 mL. Each week a different dilution was used, titrated in factors of 10 (ie, 1/10,000, 1/1000, 1/100, 1/10, 1/1), totaling 5 weeks. In the fifth week (1/1 dilution), an additional application was performed at a dose of 1.0 mL to prepare the patient for the maintenance phase (Table 1). During the maintenance phase, all doses were 1 mL with 1:1 titration. The initial maintenance schedule consisted of fortnightly or monthly injections, totaling 8 applications performed in this stage; this was followed by injections of 1 mL of the 1:1 concentration every 15, 21, or 30 days (Table 2).

Treatment began on April 2, 2019 and in a little over a month (May 9, 2019) the patient's lesions had improved by about 30%. After approximately 11 months (March 11, 2020) of desensitization, the recurrent PV was completely resolved in the cervical region, dorsum, groin, and both infra-axillary regions (Figure 2), with no adverse reactions. At the end of the protocol, given that the condition had resolved, a skin prick test was not performed to demonstrate immunological desensitization.

Discussion

Although PV generally does not involve risk of death or systemic impairment, it can cause substantial aesthetic and social discomfort for patients. Unfortunately, PV treatment failures are common due to fungal resistance, the long duration of treatment,

and the considerable side effects of antifungals.[13] Therefore, alternative and innovative antifungal strategies should be investigated as the key to future therapy, especially for cases of recurrent PV.[14]

Subcutaneous immunotherapy changes several types of antibodies specific to the injected antigen, causing serum antigen-specific IgG levels to increase. These remain increased during therapy and for several weeks or months after its end. The presence of *Malassezia* yeast cells in the skin stimulates higher production of interleukin-8 (IL-8) and interleukin-1.[15]

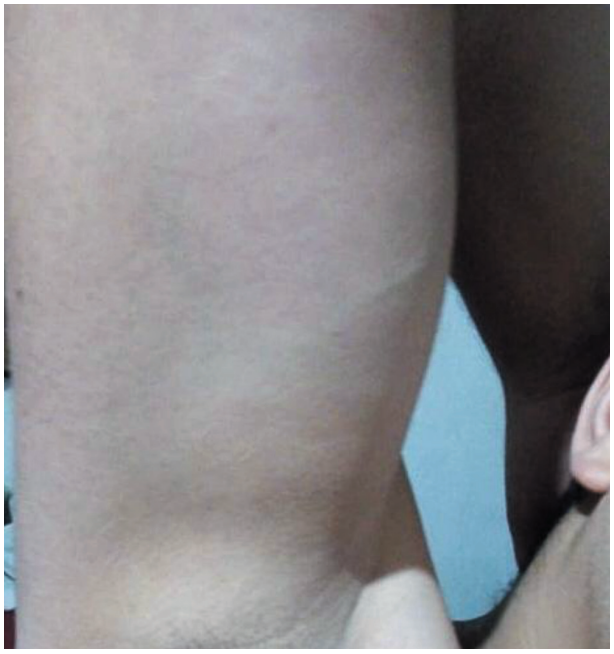

Figure 2
Right infra-axillary region after treatment, with no apparent lesions

In the present case, the patient did not respond well to topical agents, which are the treatment recommended in the literature. Similar cases were observed in a study of the main topical and systemic antifungal treatment regimens for recurrent PV; these treatments were not completely successful since the lesions remained.[9,14]

Although an elevated inflammatory state is not characteristic of PV, there is evidence of interaction between the species and the innate and specific immune response. Thus, since the antifungal immune response is physiologically marked by activation of the IL-23/IL-17 axis, in addition to controlling fungal growth, it may also be involved in certain immune-mediated pathological manifestations.[15]

This is relevant for the clinical picture described in this case report, since its recurrent nature after conventional treatment calls for new therapeutic approaches. The ideal approach for this case would be a less toxic therapy involving a more targeted antimicrobial spectrum. Several experimental treatments for fungal diseases have been described in the literature, such as monoclonal antibodies, immunotherapy with cytokines,

Table 1
Weekly treatment schedule

Week	Dilution	Dose			
1	1/10.000	0.1 mL	0.2 mL	0.4 mL	0.8 mL
2	1/1.000	0.1 mL	0.2 mL	0.4 mL	0.8 mL
3	1/100	0.1 mL	0.2 mL	0.4 mL	0.8 mL
4	1/10	0.1 mL	0.2 mL	0.4 mL	0.8 mL
5	1/1	0.1 mL	0.2 mL	0.4 mL	0.8 mL

Table 2
Fortnightly schedule

Fortnight	1	2	3	4	5	6	7	8
Dilution	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
Dose	1.0 mL	1.0 mL	1.0 mL	1.0 mL	1.0 mL	1.0 mL	1.0 mL	1.0 mL

vaccines, and antimicrobial peptides, which are new biopharmaceuticals capable of preventing or treating fungal infections. Antifungal peptides stand out in this list due to their specificity, selectivity, and tolerance.

The best option in the present case was desensitization for *Malassezia* spp. However, we could find few reports or descriptions of desensitization for *Malassezia*-type fungi, and they are generally for atopic dermatitis[10] rather than PV. Thus, the present case has experimental value and promising results.

However, despite its effectiveness, this desensitization protocol is challenging due to its complexity, requiring laboratories trained in fungal isolation and immunologists trained in dilutions and desensitization. Hence, access to this type of therapy remains limited.

Another limitation is that the treatment's degree of protection cannot be measured, which is necessary to predict relapses and the desensitization time necessary for lasting remission. However, the patient has been under clinical observation since the end of desensitization in March 2020 and, at the time of publication, has suffered no recurrence.

We conclude that desensitization to *Malassezia* spp. effectively treated PV in the present case. However, this method is still limited and is not feasible for large-scale use. More extensive studies are needed to confirm its effectiveness for recurrent PV and rule out side effects.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Raphael Coelho Figueiredo
E-mail: formimp@hotmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Limpet anaphylaxis: a rare case

Anafilaxia à lapa: um caso clínico raro

Filipa Rodrigues-dos-Santos[1], Inês Falcão[1], Maria Angeles Lopes-Mata[2], Leonor Cunha[1]

ABSTRACT

Limpet (*Patella vulgata*) is a mollusk mainly found in warm coastal regions. Limpet allergy is considered rare, and few cases can be found in the literature. We describe a clinical case of limpet anaphylaxis, including *in vitro* and *in vivo* evidence of IgE mechanism involvement.

Keywords: Food hypersensitivity, anaphylaxis, limpet, shellfish hypersensitivity.

RESUMO

A lapa (*Patella vulgata*) é um molusco frequentemente encontrado em regiões costeiras com clima quente. A alergia alimentar à lapa é muito rara, com poucos casos descritos na literatura. Os autores descrevem um caso de anafilaxia à lapa, com evidência de reação de hipersensibilidade do tipo I, através de IgE específica positiva à lapa, tanto com métodos *in vivo*, como *in vitro*.

Descritores: Alergia alimentar, anafilaxia, lapa, hipersensibilidade a frutos do mar.

Introduction

The common European limpet (*Patella vulgata*) belongs to the phylum Mollusca and the class Gastropoda. Its distribution is worldwide, being abundant in the northern coast of Spain, Japan, and warm maritime regions. In Portugal, it is most abundant along the coast of the Madeira archipelago, where it is commonly used for food. Allergic reactions to limpets are very rare. They have been described in the literature in Spain and Japan[1-4], but not Portugal. The cases described in Japan refer to the great keyhole limpet, which belongs to the genus *Fissurellidae*.[1]

Case report

A 44-year-old man had been a cook for 24 years, handling fish, mussels, oysters, and shrimp with no relevant personal history. He lived and worked as a cook in Madeira Island for 6 months in 2022.

He was referred for consultation because, while living on Madeira Island, he had an episode of generalized maculopapular rash with associated pruritus and angioedema of the lips, laryngeal tightness, and dyspnea 1 hour after ingesting 15 grilled limpets. He denied having any signs/symptoms in other systems. He denied exposure to drugs, exercise, infection, or dehydration. He went to the emergency department, where he received oral corticosteroids and antihistamines, which completely resolved the symptoms in about 6 hours. During the consultation, the emergency service charts were unavailable, as was information about the tryptase reaction. He denied any further ingestion or handling of limpets. He continues to eat shrimp, lobster, mussels, crab, octopus, and squid with no allergic reactions. He doesn't like snails and has never reacted to them.

In the immunoallergology study, skin prick tests (mm) were negative for shrimp, clams, squid, and

1. Centro Hospitalar Universitário de Santo António, Immunoallergology - Porto, Portugal.
2. LETI Pharma S.L.U., Tres Cantos, R&D Unit - Madrid, Spain.

Submitted June 20 2023, accepted June 30 2023.

Arq Asma Alerg Imunol. 2023;7(2):231-4.

http://dx.doi.org/10.5935/2526-5393.20230032-en

octopus, and prick-prick was positive for both raw and cooked limpet (histamine 9, raw limpet 13, cooked limpet 11).

The total IgE assay was 90 kUA/L and the specific IgE assay (kUA/L) for keyhole limpet was positive (1.56). It was negative for octopus (0.01), squid (0.01), clam (0.01), anisakis (0.01), and snail (0.06). Basal tryptase dosage was within normal limits (5.15 ug/L).

For the keyhole limpet sensitization study, cooked and raw keyhole limpet extracts were prepared and the protein concentration in each extract was determined using the Bradford method. The results were 176.6 µg of protein/mg of lyophilized product in the cooked keyhole limpet extract and 430.1 µg of protein/mg of lyophilized product in the raw keyhole limpet extract.

The protein profile was studied using SDS-PAGE. A 20 µg protein sample from each of the two extracts was placed in gel. The most intense band in the cooked limpet extract was approximately 35 kDa. In the raw limpet extract, a greater number of bands were distributed along the entire lane, with more intense bands appearing at 27, 45 and 90 kDa. The results are shown in Figure 1.

The allergen profile was studied by immunoblot using 20 µg of protein from both keyhole limpet extracts and patient serum diluted 1:2. The patient's IgE recognized several bands in each extract. For cooked limpet extract, bands of 15, 20, 27, 34, 39 and 55 kDa were observed. For raw limpet extract, bands of 14, 24, 27, 32, 40 kDa and 2 bands above 100 kDa were observed. The results are shown in Figure 2.

All similar studies have linked limpet allergy with sensitization to *Dermatophagoides pteronyssinus*.[5,6] For this reason, an ImmunoCAP assay with mites and tropomyosin was performed. The results are shown in Table 1.

Once the patient's sensitization to mites was confirmed, a cross-reactivity study was performed using an inhibition immunoblot assay. Cooked and raw limpet extracts were inhibited by *D. pteronyssinus* extract. The cooked limpet extract was almost completely inhibited by the mite extract. However, when raw limpet extract was used in the solid phase, inhibition by *D. pteronyssinus* extract was very slight. The results are shown in Figure 3.

In the same assay, it was confirmed that several bands in *D. pteronyssinus* extract were recognized by the patient's IgE (Figure 3, lane 2).

Keyhole limpet food allergy was diagnosed, and given the clinical presentation, the patient did not take a challenge test with keyhole limpet. The patient was prescribed an adrenaline auto-injector, oral corticosteroids, and antihistamine for emergencies. The patient currently avoids eating limpets and has not come into contact with them while cooking food. He has been asymptomatic, with no need for emergency medication. The patient's case was reported in the Portuguese Catalog of Allergies and Adverse Reactions (CPARA).

Discussion

Shellfish intake has increased worldwide in recent years[7], and may be responsible for severe allergic reactions in sensitized individuals.[8,9] Worldwide, the prevalence of shellfish food allergy is estimated to be

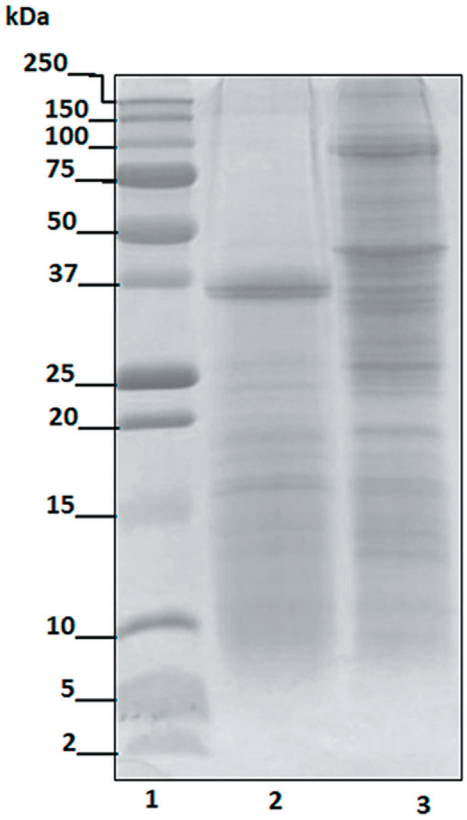

Figure 1
Protein profile (SDS-PAGE).
1 = Precision Plus molecular weight marker (Bio-Rad); 2 = boiled limpet (20 µg of protein); 3 = raw limpet (20 µg of protein).

3%.[1] However, few cases of IgE-mediated food allergy to limpets have been reported in the literature, even in regions where consumption is regular, such as the Madeira archipelago and the Canary Islands.

We have described the involvement of an IgE-mediated mechanism in an immediate reaction after limpet consumption. Unlike most reactions described in the literature, in which the main symptom after ingestion of keyhole limpet is exacerbated asthma[2,3,9], the present case involved an IgE-mediated anaphylaxis reaction. Keyhole limpet sensitization has been observed for both cooked and raw limpets, and in both cases is caused by various proteins ranging in size from 15 to over 100 kDa. Despite the scant information available in the literature on keyhole limpet allergy, several bands associated with sensitization to this food have been reported.[5,6] In these publications, keyhole limpet allergy was associated with dust mite cross-reactivity, so *D. pteronyssinus* sensitization was studied. We determined that the patient was indeed sensitized to dust mites. Positive allergenic activity for both raw and cooked limpets suggests that the implicated antigen(s) are temperature stable.

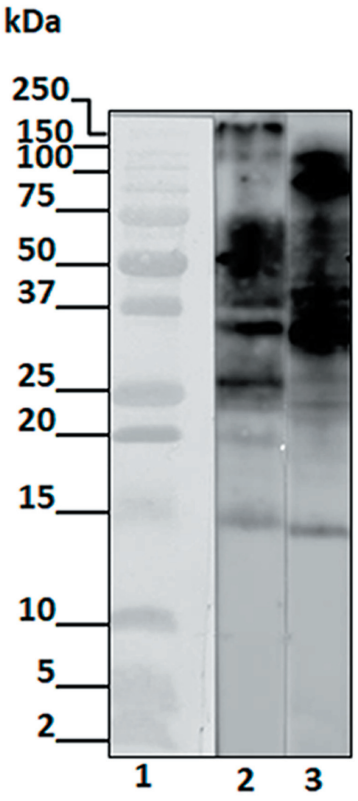

Figure 2
Allergen profile (Immunoblot)
1 = Precision Plus molecular weight marker (Bio-Rad); 2 = boiled limpet (20 µg of protein); 3 = raw limpet (20 µg of protein), serum diluted 1:2.

The patient tolerated other mollusks and crustaceans, which has been previously observed by Carrilo et al.[11], suggesting a different pattern of sensitization from that usually observed in shellfish food allergy, in which patients often present with concomitant sensitization to crustaceans and mollusks or sensitization between crustaceans.

Snails (terrestrial and marine) are also part of the gastropod class, and cross-reactivity between snails and house dust mites has been described.[10] To date, there is no description in the literature of cross-reactivity between snails and limpets, which could, however, be theoretically possible, since they belong to the same class. In our case, the patient does not eat snails, so it was not possible to assess a concomitant food allergy reaction to snails.

IgE-mediated shellfish allergy usually persists throughout life, and the only effective treatment is avoidance.[12,13] The patient continues to avoid limpets. Since he works as a cook and due to the

Table 1
Mite-specific IgE and tropomyosin

	D. pteronyssinus	*D. farinae*	Der p 10	Pen a 1
sIgE (kU/L)	15.2	8.85	0.01	0.01

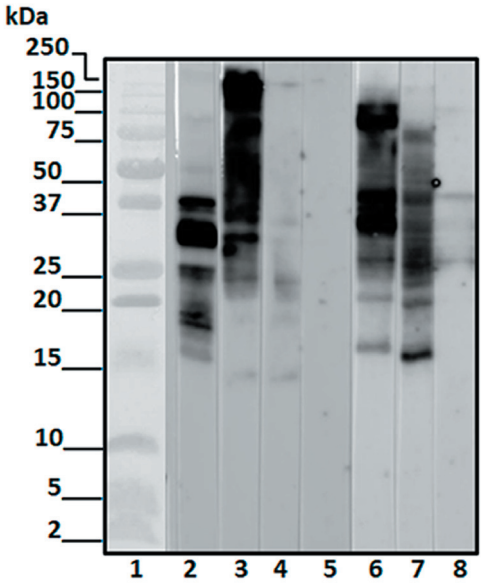

Figure 3

Cross-reactivity (Immunoblot inhibition)

M = Precision Plus molecular weight marker (Bio-Rad).

1 = *D. pteronyssinus* (20 µg protein); 2-4 = cooked limpet (20 µg protein); 6-8 = raw limpet (20 µg protein); 3 and 6 = no inhibition; 4 and 7 = inhibited with 100 µg of *D. pteronyssinus* protein; 5 = inhibited with 100 µg of cooked limpet protein; 6 = inhibited with 100 µg of raw keyhole limpet protein. In all bands, serum was diluted 1:2.

severity of the reaction, he was advised to also avoid handling limpets to prevent further reactions, whether by contact or inhalation. He was advised to wear personal protective equipment while working and carry an adrenaline auto-injector and other emergency medication with him. The patient's case has been reported in CPARA.

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No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Filipa Rodrigues-dos-Santos
E-mail: filipair.santos@gmail.com

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Delayed laryngeal edema after administration of the SARS-CoV-2 bivalent messenger RNA vaccine

Arq Asma Alerg Imunol. 2023;7(2):235.
http://dx.doi.org/10.5935/2526-5393.20230033-en

Dear Editor,

Anaphylaxis is a rare adverse reaction to the messenger RNA (mRNA) COVID-19 vaccines, and the most common event is delayed cutaneous reaction.[1-3] It must be outlined that the benefits of receiving the COVID-19 vaccines outweigh the risk of any extremely rare adverse reaction for most individuals.

There is only one report of 3 distinct cases of delayed angioedema, with suggestive laryngeal edema, occurring after the administration of the original monovalent mRNA COVID-19 vaccine (Pfizer BioNTech). All patients denied a previous history of angioedema and had no potential triggers before the onset of symptoms. All 3 patients had an atopic history of rhinitis, and 2 had asthma. Two individuals had acute urticaria as well. Two patients developed delayed angioedema after the first vaccine dosage. All required epinephrine, corticosteroid, and antihistamine administration. The mean time to symptom development was 39 hours. Serum tryptase and C4 levels were normal in 2 patients, and not collected in 1. All of them were treated in the emergency department (ED), and their angioedema completely resolved within 24 hours.[4]

A 68-year-old White woman, with a history of chronic rhinitis and asthma, tolerated well 4 COVID-19 vaccines (2 CoronaVac and 2 Pfizer-BioNTech), without adverse symptoms. One year later, she received a Pfizer-BioNTech bivalent booster, and 24 hours later she developed laryngeal edema (throat tightening with intense difficulty breathing), without facial or tongue angioedema, wheezing, or urticaria. There were no previous similar episodes and no triggers before symptom onset. She was promptly evaluated in the ED. Intramuscular epinephrine was not administered because the patient's acute respiratory distress spontaneously and steadily improved, and the laryngeal stridor finally disappeared. She was started on intravenous corticosteroid and antihistamine and maintained overnight in the hospital for close observation. Serum tryptase was not measured. On the next day, she was discharged asymptomatic using her regular asthma and rhinitis medication. No further episodes of laryngeal edema were reported in the subsequent month.

To our knowledge we are presenting the first case of delayed laryngeal edema after bivalent mRNA COVID-19 vaccination, with prompt and complete recovery.[5]

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No conflicts of interest declared concerning the publication of this letter.

Mario Geller
Geller Allergy and Immunology Clinic - Rio de Janeiro, RJ, Brazil.

Acute stress disorder and asthma: where would it be in the emergency room?

Arq Asma Alerg Imunol. 2023;7(2):236-7.
http://dx.doi.org/10.5935/2526-5393.20230034-en

Dear Editor,

Asthma, a heterogeneous disease normally characterized by chronic airway inflammation, involves a history of respiratory symptoms, such as wheezing, chest tightness, and cough, which vary in intensity and are associated with some degree of expiratory airflow limitation. Patients with infrequent symptoms may experience a severe or even fatal exacerbation that is often unpredictable and could be triggered by viral infection, allergen exposure, air pollution, or stress.[1]

Acute stress disorder (ASD) is a distinct condition that can increase antigen-specific cellular immune response and is often associated with acute asthma exacerbation. ASD can be triggered by physical or psychological stressors.[2]

To be diagnosed with ASD, individuals must have been exposed to a serious traumatic event, described as "experiencing or witnessing situations involving death, risk of death, or serious damage to their own physical integrity or that of others", ie, this experience involves intense fear, impotence, or horror.[3]

During more severe asthma attacks, the patient may experience anxiety, agitation, diaphoresis, altered brain function, dyspnea, and cyanosis. Thus, in the clinical history it can be particularly difficult to determine which specific situation triggered the ASD and panic attack.

Patients and clinicians often interpret "mild asthma" as having no risk and no need for control treatment. However, over 30% of asthma deaths occur in patients with infrequent symptoms. Therefore, due to the risk of severe exacerbation, it may be best to avoid this term.[1]

There is evidence that ASD and anxiety are associated with elevated levels of exhaled nitric oxide, which is used as a marker of airway inflammation in asthma.[4] During an attack, the patient may suffer dyspnea and an altered level of consciousness, difficulty speaking, and even vomiting, making it difficult to obtain a clinical history, thus confusing panic attacks with asthma.[1] Stress is often associated with asthma exacerbation. An individual's perception usually causes activation of the hypothalamic-pituitary-adrenal axis and subsequent release of glucocorticoids and catecholamines. The effect of these hormones on asthma is complex, since stress has been shown to both increase and attenuate symptoms.[1,2] The fact that different types of stressors (physical vs psychological) can elicit different biochemical and physiological responses may partially explain some differences in atopic disease. The duration of a stressor can also affect immune response. Although a cell-mediated immune response can be increased in ASD, the same stressor, when chronic, can suppress it.[2]

Vocal cord dysfunction, ie, inappropriate adduction (closing) during inspiration and sometimes during expiration, can mimic asthma and is thus a confounding factor. Vocal cord dysfunction should be evaluated during an ASD episode, since it has been associated with conversion disorder.[5] It can be diagnosed through direct laryngoscopy by visualizing paradoxical movement in the vocal cords, which cannot be fully explained as a physical disorder. However, certain triggers, such as gastroesophageal reflux or chemical irritants, should be ruled out.

In asthma, psychological stress has genetic and epigenetic repercussions in that it influences β2-adrenergic and glucocorticoid receptors, decreasing response to these drugs. Changes in respiratory function are also involved, including worsening obstruction and inflammation, which can be identified through a decrease in forced expiratory volume in 1 second and an increase in exhaled inflammatory gases in allergic asthma.[6] However, it is important to note that asthma is not primarily a psychosomatic illness.[1]

Decades ago, while I was interning at the Division of Allergy and Clinical Immunology of the University of South Florida/Veterans Administration Hospital (Tampa, FL, USA), Korean War veterans who were asymptomatic for asthma reported "severe attacks" during combat or on high-risk missions. The question had not yet been formulated: "Was it asthma or vocal cord dysfunction due to ASD?" This striking example could be transferred our current context.

The clinical presentation of vocal cord dysfunction varies widely, and may include laryngeal stridor, tightness in the throat, dyspnea, and dysphonia associated with various triggers, including ASD. It does not respond to conventional asthma treatment and is rarely suspected during periods of stress.[5]

When ASD is associated with asthma, long-term benzodiazepine use may be contraindicated, since they could

be iatrogenic.[3] Psychiatric evaluation and follow-up are suggested. During the consultation, doctors should "hear, rather than listen, to the patient", that is, what the patient feels and wants to communicate, regardless of whether or not they have a background in psychiatry.[7]

In difficult-to-control asthma, the purpose of the protocols is to guide physicians; they do not rule out the idea of personalized medicine.[8]

Thus ASD, associated with acute and severe asthma in asymptomatic patients, should not be seen as an "orphan entity". It warrants more thorough investigation.

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No conflicts of interest declared concerning the publication of this letter.

Francisco Machado Vieira
Department of Ocular Allergy, Brazilian Allergy and Immunology Association (ASBAI). Clínica de Alergia e Imunologia, Caxias do Sul, RS, Brazil.

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Rua Montreal, 11 – Jardim das Américas
CEP 78060-648 – Cuiabá – MT – Brazil
Tel.: 55 (65) 99229-1492

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Avenida Hiroshima, 773 – Carandá Bosque
CEP 79032-050 – Campo Grande – MS – Brazil
Tel.: 55 (67) 3047-6701

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Avenida Pasteur, 40 - Sala 208 – Santa Efigênia
CEP 30150-290 – Belo Horizonte – MG – Brazil
Tel.: 55(31) 3226-2246 | E-mail: asbaimg@asbai.org.br

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Rua dos Mundurucus, 3100 – Sala 2101 – Guamá
CEP 66073-000 – Belém – PA – Brazil
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CEP 58400-180 – Campina Grande – PB – Brazil
Tel.: 55 (83) 3066-5733 | E-mail: asbaipb@asbai.org.br

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Rua Cândido Xavier, 575 – Água Verde
CEP 80240-280 – Curitiba – PR – Brazil
Tel.: 55 (41) 3014-4413 | E-mail: asbaipr@gmail.com

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Rua José de Alencar, 725 – Boa Vista
CEP 50070-030 – Recife – PE – Brazil
Tel.: 55 (81) 3221-7676

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CEP 64051-070 – Teresina – PI
Tel.: 55 (86) 3233-4700

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Rua Siqueira Campos, 43, s. 927/928 – Copacabana
CEP 22031-070 – Rio de Janeiro – RJ – Brazil
Tel.: 55 (21) 2256-4256
E-mail: asbairj@asbairj.org.br

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Rua Raimundo Bastos da Silva, 3606 - Bl. A - ap. 901
CEP 59064610 – Natal – RN – Brazil
Tel.: 55 (84) 99169.2875

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Ethics and Professional Defense: Susana L.R. Frasson

Praça Dom Feliciano, 39, conj. 503 - Centro Histórico
CEP 90020-160 – Porto Alegre – RS – Brazil
Tel.: 55 (51) 3225-6927
E-mail: asbairs@asbai.org.br

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Rodovia José Carlos Daux, 3854 – Saco Grande
CEP 88032-005 – Florianópolis – SC – Brazil
Tel.: 55 (47) 99214-8220
E-mail: asbaisc@asbaisc.org.br

São Paulo

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Scientific: Rosana Câmara Agondi
Ethics and Professional Defense: Octavio Grecco

Rua Domingos de Morais, 2187, Bloco Xangai,
3º andar, sala 317 – Vila Mariana
CEP 04035-000 – São Paulo – SP – Brazil
Tel.: 55 (11) 5575-6888
E-mail: regionalsp@asbai.org.br

Sergipe

President: Nayra Valdete Andrade Vasconcelos
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Rua Campos, 671 – São José
CEP 49150220 – Aracajú – SE – Brazil
Tel.: 55 (79) 2105-2600

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Diretora Scientific: Raquel Prudente de C. Baldaçara
Ethics and Professional Defense: Lorena Carla Lucena

Rua 13 de Maio, 285 – Centro
CEP 77600-000 – Paraíso do Tocantins – TO – Brazil
Tel.: 55 (63) 3602-6764
E-mail: asbaito@asbai.org.br

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