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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Childhood asthma: is adherence to treatment essential for achieving control?

Asma na infância: a adesão ao tratamento é fundamental para atingir-se o controle?

Dirceu Solé[1]

In recent decades, both the prevalence and severity of allergic diseases have increased worldwide and in all age groups, especially in childhood. Asthma remains the most prevalent chronic lung disease in children and adolescents and requires special care, especially regarding asthma education. Although new asthma phenotypes and endotypes have been increasingly identified with the aim of providing a more effective and lasting targeted therapy, disease control is still the ultimate goal of asthma treatment.[1]

The scientific literature unanimously agrees that poor adherence to asthma treatment by patients is the main cause of exacerbations and poor disease control, which results in high health care costs and has been identified as a factor responsible for asthma deaths.[1] According to the Global Initiative for Asthma (GINA), symptom reduction and minimization of future risks of unfavorable outcomes are the main focus of asthma control assessment. This assessment should be conducted every 4 weeks and seek to identify possible risk factors for exacerbations, persistent airflow limitation (lung function assessment at specific times), adherence to the established therapeutic regimen, and drug side effects.[1]

The GINA also recommends that follow-up consultations for patients with asthma should assess the level of symptom control and whether the inhalation technique is adequate, monitor adherence to the prescribed regimen and adverse effects, verify if the patient is following the written action plan, and identify current attitudes/behaviors and goals to be achieved in relation to asthma. The presence of comorbidities (rhinitis, rhinosinusitis, gastroesophageal reflux, obesity, depression/anxiety, among others) should also be assessed.[1]

When faced with a patient with poorly controlled asthma, evaluating the factors that may contribute to poor treatment adherence is crucial, especially (a) factors related to the medication/treatment regimen (difficulties using inhaler device, multiple times per day, multiple different inhalers); (b) unintentional poor adherence (misunderstanding about instructions/recommendations for medication use, forgetfulness, absence of daily routine, cost); and (c) intentional poor adherence (perception that treatment is not necessary, denial or anger about asthma or its treatment, inappropriate expectations about treatment/disease, concerns about side effects, dissatisfaction with health care providers, stigmatization, cultural or religious issues, cost).[1]

The method used to quantify patients' adherence to a proposed regimen with the aim of detecting poor treatment adherence and promoting changes in this modifiable behavior should also be carefully considered. Several methods have been proposed to assess/monitor adherence to asthma treatment

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in adults and children, such as: (a) subjective assessment tools – medical assessment, family/patient assessment, self-report questionnaires such as the Morisky Scale and the Medication Adherence Report Scale for Asthma (MARS-A); (b) objective tools such as prescription data, canister weight, dose counter, directly observed therapy, and nurse-led home visits; and (c) electronic monitoring devices (DOSER CT®, SmartInhalers®, Propeller Health or Asthmapolis Device®, Inhaler Compliance Assessment device). It should be noted that these methods have several flaws, and even gold standard methods such as electronic monitoring devices have limitations.[2,3]

In this issue of the Arquivos de Asma, Alergia e Imunologia, a cross-sectional observational study assessed the importance of asthma treatment adherence in a pediatric population (n = 98) who received care in an experienced center for at least 6 months and associated it with disease control (82% of patients had moderate-to-severe asthma) and other clinical variables.[4] Questionnaires on medication adherence (MARS-5, simplified version),[2] environmental control,[5] and popular beliefs about asthma[6] were used during follow-up assessments, in addition to asthma control assessment by the Asthma Control Test (ACT).[7]

Study participants, who mostly had moderate-to-severe asthma, were being treated with inhaled corticosteroids, were polysensitized, were instructed on environmental control, and were encouraged to practice physical activities.[4] Treatment adherence was lower among patients who believed in one or more myths about asthma and its treatment. Adequate adherence to environmental control measures was identified in 51% of patients. Complete control of asthma as assessed by the ACT was significantly associated with adequate medication adherence.[4]

The study shows that despite continuous reinforcement of the therapeutic measures (environmental control, medications, physical activity, mental health, among others) recommended during patient follow-up in experienced centers, the rates of treatment adherence are good, but not optimal. The adherence rate was certainly influenced by asthma-related beliefs and myths, as pointed out by the authors. In this sense, the decision on the choice of medication (inhalation, device), if shared with the patient and their family, should improve patient safety and confidence in the treatment. This act reflects the key role of asthma education, especially for children.

In conclusion, despite recent advances in the monitoring of asthma treatment adherence, there is still a long way to go to develop an optimal monitoring tool. Adapted and validated self-monitoring questionnaires for young children with asthma, in addition to more objective measures, are still needed for routine health care practices that are hard to obtain.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Update on hypersensitivity reactions to nonsteroidal anti-inflammatory drugs – Part 1: definitions, pharmacology, epidemiology, pathophysiology, and genetics

Atualização em reações de hipersensibilidade aos anti-inflamatórios não esteroidais – Parte 1: definições, farmacologia, epidemiologia, fisiopatologia e fatores genéticos

Marcelo Vivolo Aun[1,2], Rosana Câmara Agondi[2], Diogo Costa Lacerda[2], Ullissis Pádua Menezes[3], Maria Inês Perelló[4], Adriana Teixeira Rodrigues[5], Ana Carolina D'Onofrio-Silva[2], Tânia Maria Gonçalves Gomes[6], Luiz Alexandre Ribeiro da-Rocha[7], Denise Neiva Santos de Aquino[8], Fernanda Casares Marcelino[9], Gladys Queiroz[7], Maria Fernanda Malaman[10], Inês Cristina Camelo-Nunes[8], Mara Morelo Rocha Felix[11,12,13]

ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications worldwide and the drugs most frequently associated with the occurrence of hypersensitivity reactions in Latin America. The clinical presentation of the reactions varies widely, which makes them difficult to treat. In this review, we address pharmacological aspects of NSAIDs, as well as the definitions, epidemiology, and pathophysiology of hypersensitivity reactions to NSAIDs. Finally, we discuss genetic factors associated with intolerance and allergy to these drugs.

Keywords: Nonsteroidal anti-inflammatory agents, hypersensitivity, pharmacology/pathophysiology, genetics.

RESUMO

Os anti-inflamatórios não esteroidais (AINE) estão entre os medicamentos mais utilizados no mundo e são os fármacos mais frequentemente associados à ocorrência de reações de hipersensibilidade na América Latina. As reações têm grande variabilidade de apresentações clínicas e, consequentemente, com abordagem terapêutica difícil. Nesta revisão, abordamos aspectos farmacológicos dos AINE, bem como as definições, epidemiologia e fisiopatologia das reações de hipersensibilidade aos AINE. Por fim, discutimos aspectos genéticos associados à intolerância e alergia a esses fármacos.

Descritores: Anti-inflamatórios não esteroidais, hipersensibilidade, farmacologia/fisiopatologia, genética.

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Introduction and definitions

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used medications worldwide, are often seen in prescriptions, and may be sold without prescription. They are used in the treatment of pain, inflammatory processes, and fever.[1] NSAIDs include a varied group of medications that may be classified according to their chemical structure.[2]

NSAIDs have an analgesic, anti-inflammatory, and antipyretic effect resulting from blockade of the cyclooxygenase (COX) enzyme and subsequent inhibition of eicosanoid biosynthesis through the metabolic route of arachidonic acid (AA) cascade. Moreover, NSAIDs promote inhibition of prostanoids, AA derivatives, which would be converted into prostaglandin (PG) G2 (PGG2) and H2 (PGH2) as a result of COX activity. This prevents PGH2 from being metabolized by terminal synthase in biologically active prostanoids. This inhibition leads to a decrease in vasodilation, vascular permeability, pain, and fever produced by PG.[3]

There are at least two COX isoforms. COX-1 is constitutively expressed by specific cells such as platelets and endothelial cells. COX-2, in turn, is inducible by pro-inflammatory mediators in a wide variety of cells. NSAIDs may act in the inhibition of only one COX, or in the inhibition of both.[4]

According to the World Allergy Organization (WAO), the term hypersensitivity may be applied to any reaction that can be reproduced through an initial stimulation.[5] When an individual presents with any reproducible symptom similar to an "allergic" reaction after drug stimulation, it is possible to say that a hypersensitivity drug reaction (HDR) occurred. HDRs may be promoted by specific immunological mechanisms (allergic or immunological HDR) or not (non-allergic or non-immunological HDR).[6]

NSAIDs are one of the main causative agents of HDR. In this group of drugs, there is a remarkably high variety of clinical pictures and pathophysiological mechanisms involved. Consequently, in times of precision medicine, knowing these different scenarios will make it possible to perform the correct management of these patients, especially with regard to future guidance to prevent new reactions, but also to approve medications that would not need to be excluded. In this review, we discuss conceptual, epidemiological, genetic, and pathophysiological aspects of hypersensitivity to NSAIDs.

Mechanism of NSAID pharmacological action

Before 1971, little was known about the NSAID mechanism of action, except that these drugs produced an anti-inflammatory effect different from the anti-inflammatory action of corticosteroids. Many of the biochemical effects of NSAIDs were documented,[7] but theories based on these effects were abandoned. The most reasonable hypothesis at that time was based on the observation that salicylates could inhibit several proteases. Increased extracellular proteolytic activity was observed in several inflammation models, and this was thought to be responsible for tissue destruction, a typical feature of chronic diseases such as rheumatoid arthritis.[8] NSAIDs are a class of medications used as antipyretic, anti-inflammatory and analgesic agents.[9]

Inflammatory response consists of a vascular reaction and a cell reaction. Many cells are involved in inflammation, such as neutrophils, monocytes, eosinophils, lymphocytes, basophils, platelets, connective tissue cells, including mast cells surrounding blood vessels, connective tissue fibroblasts, local macrophages, and lymphocytes. This inflammatory response may be acute or chronic. The first, characterized by local vasodilation and increased capillary permeability, is a very rapid inflammatory process, because the response is shorter and may last for minutes, hours, or days. The latter, in turn, is characterized by presenting a longer duration and is associated with the presence of lymphocytes and macrophages and with proliferation of blood vessels, fibrosis, and tissue necrosis.[10]

The main NSAID mechanism of action is inhibition of the COX enzyme, or, in a more complete way, of the so-called prostaglandin endoperoxide synthase (PGHS) complex. COX is necessary to convert AA into thromboxanes (TXs), PG, and prostacyclins.[11] The therapeutic effects of NSAIDs are attributed to the lack of these eicosanoids. Specifically, TXs play a role in platelet adhesiveness, whereas PGs cause vasodilation, increase hypothalamic temperature set point, and play a role in nociception.

There are two COX isoenzymes: COX-1 and COX-2 (PGHS -1 and PGHS-2, respectively). COX-1 is constitutively expressed in the body and plays a role in the maintenance of gastrointestinal mucosal coating, renal function, and platelet aggregation. COX-2 is not constitutively expressed in the body. Conversely, it is inducibly expressed during an inflammatory response. Most NSAIDs are not selective for one of the isoenzymes and inhibit both COX-1 and COX-2.

However, COX-2-selective NSAIDs (named "coxibs") aim to inhibit only COX-2, and thus have a different profile of adverse effects. It is important to emphasize that, since COX-1 is the main mediator to ensure gastric mucosal integrity and COX-2 is especially involved in inflammation, COX-2-selective NSAIDs should provide anti-inflammatory relief without compromising the gastric mucosa.[11,12]

Nevertheless, emerging evidence challenges the theory that COX-2-selective inhibitors are safer. In the early 2000s, there were the first reports of cardiovascular adverse effects associated with COX-2 inhibitors, and subsequent placebo-controlled studies also showed that these inhibitors were related to increased risk of atherothrombotic vascular events.[13] Moreover, meta-analyses and randomized clinical trials further confirmed these findings, which led the US Food and Drug Administration (FDA)[14] and, subsequently, other regulatory agencies, such as the Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA), to withdraw approval for several COX-2 inhibitors. In addition to gastrointestinal and cardiovascular complications, the routine use of NSAIDs is also associated with nephrotoxicity and potential renal failure,[15] along with other transient effects on fluid and electrolyte balance.

The existence of a third COX isoform, named COX-3, has been recently proposed, which, contrary to COX-1 and COX-2, would produce anti-inflammatory chemicals rather than pro-inflammatory prostanoids, a fact that could explain the remission of some chronic inflammatory diseases such as rheumatoid arthritis. COX-3 is expressed in the brain, the spinal cord, and the heart.[16]

Classification based on chemical groups

Traditionally NSAIDs were classified on the basis of their chemical characteristics wherein most of the popular NSAIDs are categorized as major derivatives of salicylic acid, acetic acid, enolic acid, anthranilic acid, or propionic acid. However, with the advancement of scientific knowledge, the classification has also been shifted based on their selectivity for inhibiting COX-1 and COX-2 enzymes. In addition, a classification system has also been formulated to categorize NSAIDs on the basis of their half-life. Nevertheless, despite the interclass diversity, their functions are relatively similar.[17]

Based on their chemical structure, NSAIDs may be broadly classified into salicylates, aryl and heteroaryl acetic acid derivatives, indole/indene acetic acid derivatives, anthranilates, and oxicams (enol acids) (Figure 1).[14,18] The general structure of a typical NSAID consists of an acidic moiety (carboxylic acid, enols) attached to a planar aromatic functional group. Salicylates were the first identified NSAIDs following extraction of salicylic acid from willow bark.[7] They are actually derivatives of 2-hydroxybenzoic acid (salicylic acid). Initially, salicylic acid was medicinally used in the form of sodium salt; later, this compound got replaced therapeutically by the acetylated derivative, acetylsalicylic acid (ASA) or aspirin.

After salicylates, aryl and heteroaryl acetic acid derivatives constitute an important class of NSAIDs. Ibuprofen, ketoprofen, and naproxen are some structural derivatives of aryl and heteroaryl acetic acids which comprise some of the most popular NSAIDs. The next category of NSAIDs is indole or indene acetic acid, which includes popular pain killers, such as indomethacin and sulindac. Moving further, anthranilates are another class of NSAIDs which are N-aryl substituted derivatives of anthranilic acid. Diclofenac, the derivative of 2-aryl acetic acid, is the most widely used anthranilate NSAID, being found in diverse formulations, including pain killer tablets, injections, topical presentations, and fast acting sprays. Mefenamic acid and meclofenamic acid are also derived from anthranilic acid. Finally, there are enol acid derivatives, such as oxicams (tenoxicam, piroxicam, meloxicam) and pyrazolones (dipyrone).[14,18] The classification of NSAIDs by pharmacological group is synthesized in Figure 1.

Classification of NSAIDs based on the selectivity of COX isoenzyme

Bioconversion of AA into inflammatory prostanoids is mediated by COX-1 and COX-2 enzymes, which, in turn, are inhibited by NSAIDs. Almost all the NSAIDs variably inhibit both the COX isoforms at their therapeutic doses. Thus, on the basis of COX selectivity, an inhibitory ratio is determined, which allows a classification of NSAIDs. The inhibitory ratio is based on the COX-1 IC_{50}/COX-2 IC_{50}. If the ratio is 1, then both the PGHS enzymes are equally inhibited by the concerned NSAID; if the ratio is less than 1, it means that the concerned NSAID is less selective for COX-2 compared to COX-1, and in case of ratio

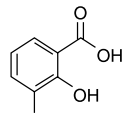
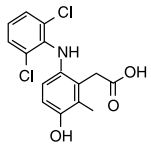
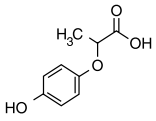
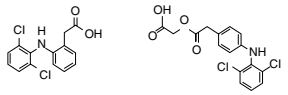
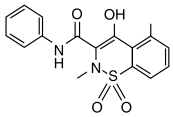
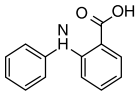
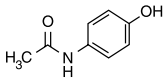
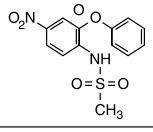
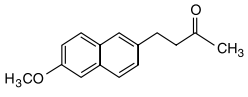
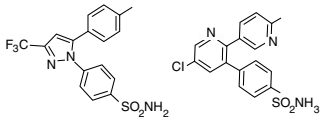
Pharmacological group	Basic chemical structure	Examples of drugs
Salicylic acids		Acetylsalicylic acid (ASA, aspirin), diflunisal, salsalate
Carbo and heterocyclic acetic acids		Indomethacin, ketorolac, etodolac
Propionic acids		Ibuprofen, ketoprofen, naproxen, flurbiprofen
Phenylacetic acids	 Diclofenac Aceclofenac	Diclofenac, aceclofenac
Enolic acid derivatives - Oxicams		Piroxicam, tenoxicam, meloxicam
Enolic acid derivatives - Pyrazolones		Dipyrone, phenylbutazone
Fenamic acids		Mefenamic acid, flufenamic acid, meclofenamate
Para-aminophenol derivatives		Paracetamol (acetaminophen)
Pyridinic sulfonamide		Nimesulide
Naphthyl alkanone		Nabumetone
Diaryl heterocyclic acids (“coxibs”)	 Celecoxib Etoricoxib	Celecoxib, etoricoxib, valdecoxib

Figure 1
Classification of non-steroidal anti-inflammatory drugs according to pharmacological group and chemical structure
(modified from Blanca-Lopez N, et al.[18])

greater than 1, the NSAID is preferentially selective for COX-2.[19]

It is presumed that the side effects of NSAIDs, such as gastrointestinal manifestations, are associated with COX-1 inhibition, while therapeutic effect (anti-inflammatory) is correlated with that of COX-2, and often a high level of PG suppression is needed for therapeutic relevance. However, this simplistic view has been questioned recently. In general, NSAIDs are therapeutically employed at doses that generate more than 50% reduction of PG production. In this context, it would be important to check the extent to which COX-1 gets inhibited at the same concentration of NSAID that is required for inhibiting 80% of COX-2 activity. However, in the case of diclofenac, the concentration which inhibits 80% of COX-2 activity can also inhibit almost 70% of COX-1 activity at the same time. So, therapeutic dose (80% inhibition of COX-2) can even lead to toxicity. In this scenario, when relative selectivity varies within a narrow range, other variables, including consumed dose and plasma half-life, should be considered. For example, piroxicam, which has long plasma half-life and is correlated with gastrointestinal toxicity in vivo, did not show notable COX-1 selectivity in the in vitro assay. Hence, it is clear that the relative potency of NSAIDs varies with their dose, concentration, and plasma half-life. Therefore, IC80 seems to be clinically more relevant in comparing NSAIDs' inhibitory potencies against COX-1 and COX-2.[19]

Now, on the basis of the potencies to inhibit COX isoforms, NSAIDs can be divided into four main categories (Table 1): (i) non-selective, complete inhibitors of both COX-1 and COX-2; (ii) complete inhibitors of COX-1 and COX-2, although with specific preference for COX-2; (iii) strong inhibitors of COX-2, although with weak inhibiting action against COX-1; and (iv) weak inhibitors of COX-1 and COX-2.[19] However, in terms of kinetics, NSAID interactions with both the COX isoforms can also be used for their classification, which is as follows: freely reversibly interaction (ibuprofen), slowly reversible interaction (indomethacin, diclofenac, celecoxib) and irreversible interaction (aspirin).

Two agents that show some degree of "preferential" COX-2 inhibition are meloxicam and nimesulide. For these compounds, it has been difficult to attribute a relationship of gastrointestinal "safety" when compared to the other conventional NSAIDs, since, despite preferential COX-2 inhibition, the therapeutic doses of these drugs will also result in reduced COX-1 activity.[19]

Epidemiology of hypersensitivity reactions to NSAIDs

NSAIDs are widely used worldwide for relief of pain and inflammation and are responsible for 25% of adverse drug reactions, including HR.[20] NSAIDs, together with beta-lactam antibiotics, are the leading cause of HDRs worldwide.[21] According to an American study, up to 30% of adults consume pain killers for chronic pain, a percentage that may reach 40% among those older than 65 years, either by prescription or

Table 1
Categorization of NSAIDs based on COX inhibition (adapted from Warner TD et al.[19])

Categories	COX-1 and COX-2 selective inhibition	Name of NSAIDs
I	COX-1 and COX-2	Indomethacin, aspirin, diclofenac, naproxen, ibuprofen
II	5- to 50-fold selectivity for COX-2	Meloxicam, nimesulide
III	> 50-fold selectivity for COX-2	Coxibs
IV	Poor selectivity for COX-1 and COX-2	Sulfasalazine, nabumetone

COX = cyclooxygenase, NSAID = nonsteroidal anti-inflammatory drug.

self-medication,[22] so that the use of NSAIDs without medical prescription is very common.

In the general population, the prevalence of HR to NSAIDs ranges from 0.5 to 5.7%.[2,23] Age stratification shows a significant variation with regard to gender, phenotype, and NSAID class involved. Women are the most affected among adults, although this relationship is inverse in childhood, when boys are more affected. In all ages, the most prevalent phenotype is NSAID-induced urticaria/angioedema (NIUA) in patients with no underlying disease. This phenotype accounts for 40% of HRs and for 60% of non-immunological reactions.[22] Within this group, isolated palpebral and/or labial angioedema is the most common presentation in children, with increased prevalence up to young adults, and is often related to atopy and sensitization to aeroallergens.[24] The association of cutaneous with respiratory manifestations characterizes the blended, or mixed, phenotype (30%), considered the second most common both in children (especially in adolescents) and in adults, with manifestations that appear simultaneously or sequentially.[25] The phenotypes characterized by exacerbation of respiratory disease, also known as ASA/NSAID-exacerbated respiratory disease (NERD), or exacerbation of chronic spontaneous urticaria (CSU), known as NSAID-exacerbated cutaneous disease (NECD), are more prevalent in adults, and each one accounts for 8% of total reactions. NERD occurs in up to 20% of individuals with asthma and nasal polyposis.[22] Conversely, the occurrence of NERD (asthma and/or chronic rhinosinusitis and/or polyposis) is rare in pediatric patients.[24] CSU is rare in children, and its exacerbation by NSAIDs (NECD), which fluctuates with periods of disease activity, is less frequent (24%) when compared to adults (up to 40% of those with CSU).[2,25,26]

Among patients with non-immunological hypersensitivity (NIUA, NECD and NERD), non-selective or preferential COX-1 inhibitors have a role in inducing reactions. However, even weak COX-1 inhibitors that are preferential or selective COX-2, depending on the dose, are potential triggers, since up to 1/3 of patients may present reactions with paracetamol at doses higher than 1,000 mg.[2]

The class of NSAID involved also varies in frequency according to geographic space and age group. In Americas, NSAIDs are the most prevalent cause of immediate HDR.[27] In Brazil and Latin America, they are the main cause of drug-induced anaphylaxis. Non-immunological anaphylaxis induced by NSAIDs is the most prevalent one, although IgE-mediated reactions were associated with greater severity. Furthermore, dipyrone stands out as one of the most implicated agents in these reactions in Latin America.[28-30] In the USA, ibuprofen and naproxen lead the ranking, whereas diclofenac is the most prescribed one in the United Kingdom.[22] Considering the pediatric population, o paracetamol and ibuprofen predominate, whereas other NSAIDs (diclofenac, dipyrone, "oxicams," and ASA) increase in parallel with the consumption of new drugs with increased age.[25]

Atopic diseases in adults and children are considered an important risk factor for NSAID hypersensitivity, a fact that may be related to environmental, ethnic, or genetic factors. NIUA is much more frequent among atopic patients sensitized to mites. Regarding NERD, association with atopy is still controversial. Older studies reported that it was less frequent in adults with atopy,[24] but more recent data suggest that up 75% of individuals with NERD have atopy.[30] The participation of co-factors such as infection, food allergy, and physical activity are common in the pediatric population.[26] Infections may act as a co-factor, both in immediate and non-immediate reactions, especially in children, leading to urticaria, angioedema, and maculopapular exanthema not reproducible after oral provocation tests (OPTs).[25]

Selective reactions to a NSAID or a chemically related group, with tolerance to other unrelated groups and ASA, may be immediate and manifest as single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA), a form of immediate immunologic hypersensitivity that occurs less than 1 hour after drug intake (20-30%).[22] The most medication more frequently related to this reaction is dipyrone (methimazole), but selective reactions with paracetamol, diclofenac, and ibuprofen have already been reported. Still within this group, the inclusion of a phenotype of patients with immediate selective reaction to multiple groups with tolerance to ASA was recently suggested.[24,26]

Non-immediate selective reactions, which occur more than 24 hours after consumption of the NSAID, represent a heterogeneous group of reactions of variable severity and accounting for less than 5% of total reactions.[22] These reactions, also known as single-NSAID-induced delayed hypersensitivity reactions (SNIDR), vary from mild reactions (such as maculopapular exanthema, delayed urticaria, contact

dermatitis or photodermatitis, fixed drug eruption) to the most severe ones, such as hepatitis pneumonitis, nephritis, and the so-called severe drug cutaneous reactions, such as acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalized bullous fixed drug eruption. Maculopapular exanthema, rare in adults, is more frequent in children, in the context of infections, and is often not confirmed by the OPT.[25]

Pathophysiology of HRs to NSAIDs

HRs associated to NSAIDs are divided into immunological (or allergic) reactions and non-immunological (or non-allergic) reactions. The so-called immunological reactions to NSAIDs involve mechanisms of type I (IgE-mediated) and type IV (T-cell dependent) Gell and Coombs hypersensitivity classification. Up to date there has been no documented strong evidence of type II (cytotoxic) and III (immune complex) reactions. Conversely, non-immunological reactions seem to be associated to potential of COX-1 inhibition by these drugs.[2,23]

Immunological reactions

Immunological or allergic NSAID-induced reactions may be immediate or on-immediate (delayed). Patients who present these reactions are considered selective reactors, i.e., their reactions are restricted to the causative drug or to others of the same pharmacological class.[2,18]

In immediate reactions (SNIUAA), symptoms such as urticaria, dyspnea, and anaphylaxis usually results from mast cell degranulation due to binding of the specific IgE to high-affinity IgE receptors present in mast cells. In the first contact with the antigen, there is a polyclonal increase of specific T and B cells and production of specific IgE without causing symptoms. After 5-6 days, the secreted IgE sensitizes mast cells. In the next contact, minutes after the drug was administered, mast cells undergo degranulation, with the release of various mediators, especially histamine, causing symptoms such as urticaria, dyspnea, cough, and anaphylaxis, among others. The development of the reaction does not depend on the administered dose, but it is clear that the intensity of symptoms has a strong association with drug concentration in the body. Among the different classes of NSAIDs, the occurrence of this mechanism is better documented with pyrazolones (e.g.: dipyrone), mainly through skin tests (puncture and intradermal), since in vitro assays have low sensitivity.[31]

Conversely, delayed reactions (SNIDRs) occur after longer medication use and seem to have some degree of dose-dependency. The activation of TCD4 and/or TCD8 cells is stimulated by drug use, and symptoms (e.g., exanthema) are simply a consequence of the amount of the drug, number of activated T-cells, tissue migration, and intensity of affinity to Toll-like receptor (TLR), innate lymphoid cell receptor, for the peptide-hapten complex/drug.[32]

Non-immunological reactions

Most NSAIDs perform non-selective inhibition of the COX-1 enzyme. They interfere with AA metabolism, leading to blockade of PG synthesis and to positive regulation of LT pathways, which contributes to several manifestations of HRs to NSAIDs.[33] In susceptive individuals, COX-1 inhibition causes AA metabolism disorders, 5-lipoxygenase leukotriene C4 synthase (LTC4S) dysfunction, reduced PGE2, and increased production of cysteinyl leukotriene (CysLT). Reduced levels of PGE2 pathway increase LTC4S pathway response, which enhances CysLT production. Excessive CysLT production leads to vascular extravasation, bronchoconstriction, and excessive mucus secretion, as well as activation of mast cells and eosinophils, which release chemical mediators and cytokines, further increasing systemic inflammation.[2,34,35]

This is the most common mechanism to explain HRs associated with NSAIDs and includes the phenotypes of NIUA, NECD, NERD, and even the so-called mixed (or blended) reactions, in which individuals develop anaphylaxis after exposure to more than one NSAID of different classes.[2,35]

NSAIDs that exert a predominant inhibition on COX-1 enzymes, such as ASA, naproxen, and diclofenac, have higher rates of HRs, whereas weak COX-1 inhibitors and COX-2-selective inhibitors are usually better tolerated, with lower probability of HRs.[33]

The pathophysiological mechanism proposed for non-immunological HRs to NSAIDs (NIUA, NECD and NERD) is summarized in Figure 2.

Genetic aspects

Inhibition of COX-1 activity, the therapeutic target of most NSAIDs, makes it possible to assume

the underlying mechanism for cross-intolerance to NSAIDs of various chemical structures. In this pathway, the polymorphisms in genes that involve COX and lipoxygenase pathways and leads to imbalance between PG and LT have been the focus of most studies, especially in NERD and, more recently, in NIUA.

A Spanish study in patients with NERD revealed a significant association with single nucleotide polymorphisms (SNP) in the *prostaglandin-endoperoxide synthase gene 1 (PTGS1)* (rs5789 and rs10306135), the first related to decreased enzyme activity, and the latter involved in gene expression regulation.[36] Another study identified, in two different cohorts in Spain, polymorphisms related to *PTGS1* rs10306194 and *ALOX5* rs28395868 associated with risk of NIUA, whereas the latter polymorphism was also related to respiratory manifestations exacerbated by NSAIDs, bringing hope of a potential genetic biomarker to distinguish the different phenotypes.[37]

A study that analyzed the complete PTGS sequence identified a haplotype in the *PTGS1* gene that is over-represented in patients with cross-reactive NSAID hypersensitivity and associated with severely decreased COX-1 enzyme activity in a Spanish population. Such haplotype contains two single nucleotide variations that may be also related to other adverse effects involving decreased enzyme function. However, the identification of variants in the *PTGS2* gene (COX-2) was not related to cross-reactivity to NSAIDs, consistent with the tolerance of most patients to COX-2-selective inhibitors. Although the

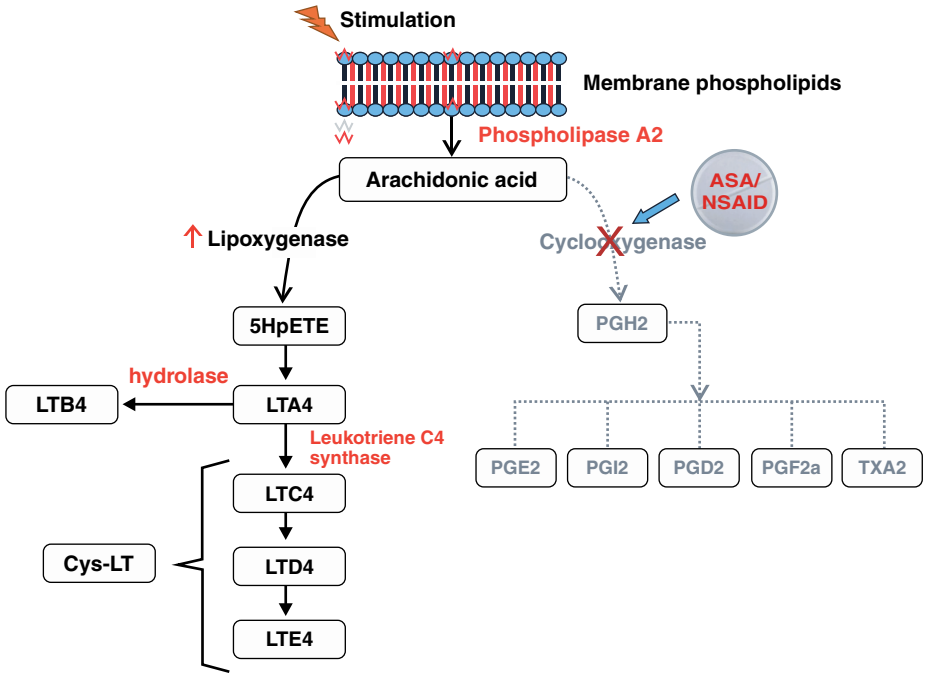


Figure 2
Pathophysiological mechanism of non-immunological hypersensitivity reactions (HR) to acetylsalicylic acid (ASA) and the remaining nonsteroidal anti-inflammatory drugs (NSAIDs), which is based on the pharmacological action of these drugs. The metabolism of arachidonic acid involves actions of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, leading to the synthesis of prostaglandins (PG), prostacyclins, thromboxanes (TX), and leukotrienes (LT). Since the main action of NSAIDs is inhibiting COX, there is a metabolic deviation for the action of LOX and, consequently increased synthesis of cysteinyl leukotriene (Cys-LT). In patients with non-immunological HRs, this accumulation of Cys-LT has a vasodilator action, induces smooth muscle contraction, and eventually cause the symptoms

Adapted from Walters KM, et al.[35]

risk haplotype was present in only a small proportion of patients (5.6%), the strong association observed and the effect of reducing enzyme activity reinforce the hypothesis of potential genetic susceptibility in the investigation of patients with family history of cross-reactive hypersensitivity to NSAIDs.[38]

The identification of polymorphisms (rs9883222, rs2298954, rs2236944) in the G protein subunit alpha I2 (*GNAI2*), located in the same haplotype at locus 3p21.31, reflect their influence in the pathological mechanisms of hypersensitivity to NSAIDs, such as LT receptor activation and recruitment of the immune cells involved. This association, identified in genome wide association studies in patients with urticaria/angioedema/anaphylaxis, was replicated in the Spanish population of two different region.[39]

Few genetic association studies, a useful tool to identify pharmacogenetic targets, were conducted in this area. These studies require large samples, not only to identify low-frequency findings that may have a relevant impact on phenotype, but also to detect disease risk.[36] A genetic association study was conducted in a Korean population to investigate genetic susceptibility to aspirin intolerance and identified the *CEP68* gene (which codifies the centrosomal protein of 68KDa) as a risk factor in asthmatics. Subsequently, the same study, in a candidate gene approach, related the rs7572857 SNP to the genetic etiology of aspirin intolerance after oral provocation in asthmatics with significant decline in forced expiratory volume in 1 second, especially related to the homozygous AA of rs7572857G >A variant.[40] In a study with a population of Spanish ancestry, 17 variants of *CEP68* were identified, including rs7572857, in patients with NIUA, 8 of which were also present in patients with respiratory manifestations, NERD, and blended reactions.[41] Another study in the Spanish population assessing the *CEP68* candidate gene found two intronic variants (rs2241160 and rs2241161) with a significantly association in patients with immediate allergic reaction, selective to a single NSAID (SNIUAA). However, no overlap was observed with genetic variants previously associated with pharmacologically mediated hypersensitivity, pointing to a complex role for this gene and its potential use in the development of biomarkers of clinical utility to diagnose patients at risk.[42]

A genetic association study in a cohort of Korean asthmatics showed SNPs in 30 regions of the HLA-DPB1 gene that were significantly associated with the risk of NERD, and rs1042151 (Met105Val) was the most important genetic variant.[43] In the Asian population, HLA-DPB1*0301 was considered a strong marker of aspirin-intolerant asthma.[44] In another Korean study, the HLA-DRB1*1302-HLA-DQB1*0609-DPB1*0201 haplotype revealed to be a potential marker for NSAID-induced cutaneous phenotypes. Furthermore, in an Italian study, HLA-B44 and HLA-Cw4 were positively associated with NECD.[36]

In this still little explored field, recent findings in a Spanish and *Han* Chinese population suggest other pathways besides AA metabolism involved in cases of cross intolerance with manifestations of urticaria and angioedema. There may also the influence of genetic variants involved in histamine metabolism, IgE receptors, and activation of cytokines, mast cells, and drug-metabolizing enzymes. It is worth highlighting that most studies were conducted in Asian and European patients and were not replicated in ethnic minority or mixed populations.[36]

Despite advancements in studies, the discovery of genetic variants that predispose individuals to hypersensitivity to NSAID is still unknown. In addition to the heterogeneity of phenotypes, there are difficulties related to the genetics of complex diseases.[26]

Conclusions

NSAIDs are both the most used medications worldwide and the most frequently associated with HRs. Knowledge of the pharmacological actions of these drugs, of the epidemiology of HRs, both in Brazil and worldwide, and of the pathophysiological mechanisms and genetic factors involved in these events is essential for allergists-immunologists to provide individualized care to their patients and to act accurately.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Adverse reactions to monoclonal antibodies in allergic diseases

Reações adversas aos anticorpos monoclonais para doenças alérgicas

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ABSTRACT

The use of immunobiological agents in allergy and immunology has increased in recent years, emerging as potentially effective strategies to treat allergic and hypersensitivity diseases. The use of immunobiological agents is recommended in the severe forms of allergic diseases, for which their efficacy, safety, and cost-effectiveness have been established. The purpose of this study was to summarize the most common or significant adverse effects, including hypersensitivity reactions to the main monoclonal antibodies approved for the treatment of allergic diseases that are currently licensed and marketed in Brazil.

Keywords: Monoclonal antibodies, asthma, drug-related side effects and adverse reactions, atopic dermatitis, urticaria.

RESUMO

A utilização de agentes imunobiológicos em alergia e imunologia tem sido cada vez mais frequente nos últimos anos, emergindo como potencialmente eficazes para o tratamento de doenças alérgicas e de hipersensibilidade. O uso de imunobiológicos em doenças alérgicas está recomendado nas formas graves onde a eficácia, segurança e custo-efetividade estão comprovados. O objetivo deste artigo é sintetizar os efeitos adversos mais comuns ou significativos, incluindo as reações de hipersensibilidade aos principais anticorpos monoclonais aprovados para o tratamento de doenças alérgicas licenciados e comercializados no Brasil até o momento.

Descritores: Anticorpos monoclonais, asma, efeitos colaterais e reações adversas relacionados a medicamentos, dermatite atópica, urticária.

Introduction

The use of immunobiological agents in allergy and immunology has increased in recent years, emerging as potentially effective strategies to treat allergic and hypersensitivity diseases.[1] In Brazil, the main immunobiological agents used in the clinical practice of allergists and immunologists are polyclonal human immunoglobulins (both intravenous and subcutaneous), used in replacement therapy

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for inborn errors of immunity or in autoimmune and inflammatory diseases, and monoclonal antibodies. The use of monoclonal antibodies is more recent and is expected to increase over the next years due to their availability for the treatment of asthma in the Brazilian Unified Health System (*Sistema Único de Saúde*, SUS) and their inclusion in the List of Procedures of the Brazilian National Supplementary Health Agency (*Agência Nacional de Saúde*, ANS). Four main classes of monoclonal antibodies are currently approved for use in allergic diseases: anti-IgE (omalizumab), anti-IL-5 (mepolizumab), anti-IL-5R (benralizumab), and anti-IL-4R/IL-13R (dupilumab).[1]

The use of immunobiological agents is recommended in severe forms of allergic diseases, for which their efficacy, safety, and cost- effectiveness have been established. Nearly 30% of patients with severe asthma depend on high doses of inhaled corticosteroid and frequent use of beta-2 agonists, often with frequent courses or continuous use of oral corticosteroids to maintain asthma control, despite of side effects[2]

Due to the impact of severe asthma, that was the first allergic disease to be treated with an immunobiological drug and is currently the condition with the greatest number of options of biological therapy.[3,4] Subsequently, other conditions, such as urticaria, atopic dermatitis (AD), and chronic rhinosinusitis with nasal polyps (CRSwNP), have started to include this class of medications in their therapeutic arsenal.[4,5]

The purpose of this study was to summarize the most common or significant adverse effects, including hypersensitivity reactions to the main monoclonal antibodies approved for the treatment of allergic diseases that are currently licensed and marketed in Brazil.[1]

Classification of adverse reactions to biological agents

Immunobiological agents demonstrate differences from traditional drugs in terms of chemistry, mode of action, metabolism, and immunogenicity. These drugs are protein complexes obtained from cultures of bacteria, yeast, insects, plants, or mammalian cells, through genetic engineering techniques. Adverse events induced by xenobiotics (traditional drugs) are mainly linked to pharmacological effects, whereas the adverse effects of immunobiological agents are often target-related and linked to the biological consequences of their action.[6]

Considering these differences, Pichler proposed an original classification of adverse reactions to immunobiological agents (Figure 1). Adverse reactions to these agents are classified into five groups: (1) Type alpha – induced by cytokine release, whose main manifestations are fever, asthenia, arthralgia, headache, myalgia, gastrointestinal symptoms, and cutaneous eruption mimicking a Sweet's syndrome; (2) Type beta – involves immediate and delayed hypersensitivity reactions linked to the immunogenicity of immunobiological agents, more frequent with chimeric antibodies, but that can also occur with humanized and fully human antibodies through anti-idiotypic antibodies; (3) Type gamma – related to immune dysregulation, including immunosuppression and autoimmunity; (4) Type delta – results from the co-expression of the target antigen on both pathological and normal tissue cells; (5) Type epsilon – related to new and unexpected non-immunological functions of immunobiological agents revealed by use in humans, such as neuropsychiatric disorders associated with interferon (IFN)-alpha and cardiac complications caused by anti-tumor necrosis factor (TNF)-alpha agents.[7]

Omalizumab

Omalizumab was the first immunobiological agent approved for the treatment of moderate-to-severe allergic asthma presenting with levels of total IgE from 30 to 1,500 IU/mL and IgE-specific sensitization to aeroallergens. It was initially approved for patients older than 12 years of age and, subsequently, for children over 6 years. It is a recombinant humanized monoclonal antibody that targets free serum IgE and, thus, prevents its attachment to mast cells and basophils and release of inflammatory mediators. Finally, this mechanism leads to downregulation of high-affinity IgE receptors (FcεRI) in these cells and inhibition of allergic reaction. Subsequently, omalizumab was approved for use in patients diagnosed with chronic spontaneous urticaria aged over 12 years and, more recently, it was approved for the treatment of severe nasal polyposis in patients over 18 years of age and with levels of total IgE from 30 to 1,500 IU/mL, regardless of the presence of aeroallergen sensitization.[8]

The most frequently reported adverse reactions were injection-site reaction (45%), respiratory

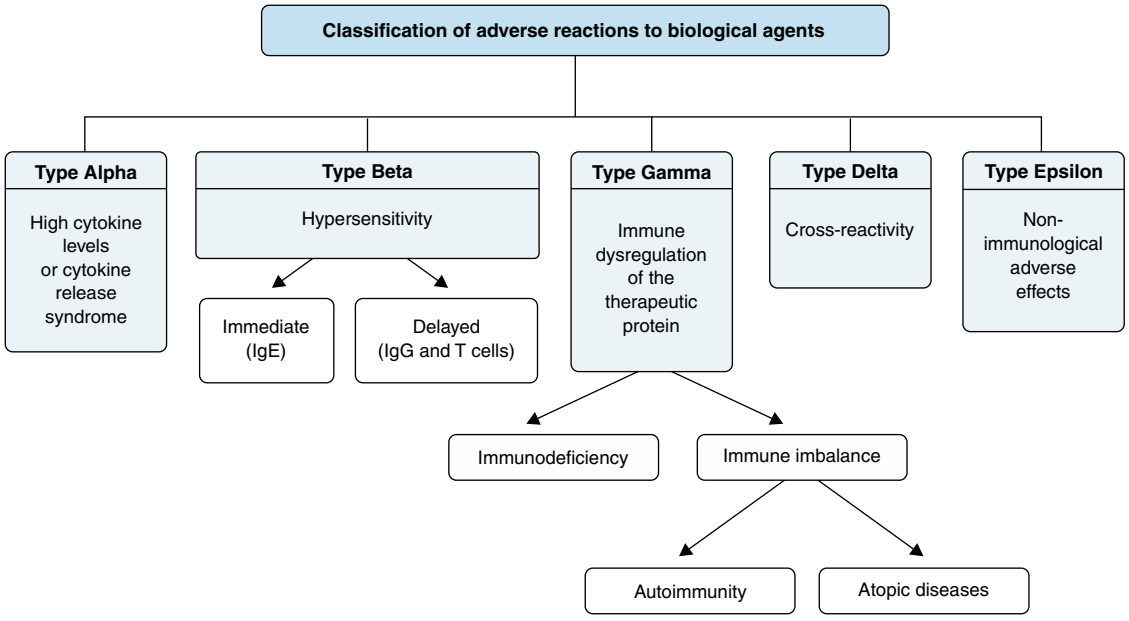

Figure 1
Classification of adverse reactions to immunobiological agents
Modified from Pichler WJ[7].

infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%).[9]

Data from 35 phase 1 to 3 studies showed an apparent increase in malignancies among omalizumab users (0.5% vs. 0.2% in controls).[10] Most consisted of solid tumors, except for a case of recurrent non-Hodgkin lymphoma. Of the 25 cases of malignancy, 4 seemed to be present before initiation of omalizumab therapy, and all cases, except for one of basal cell carcinoma, were diagnosed in the first two years of use of the biological agent. A subsequent evaluation of 32 clinical trials, conducted in 2012, did not show any association between omalizumab and risk for malignancy, which was subsequently confirmed by the Evaluating Clinical Effectiveness and Long-term Safety in Patients (EXCELS) trial.[11]

The existing literature estimates the risk of developing anaphylaxis due to omalizumab at 0.09%, with most cases (77%) occurring during the first 2 hours after administration of the first 3 doses.[12] Confirmation may be performed by skin tests with the drug diluted in saline and, if result is negative, an intradermal test with a concentration of 1: 100,000 (or 1.2 µg/mL) may be conducted to assess hypersensitivity.[13] Rarely, a desensitization may be required.[14] Another possibility is sensitization to other chemicals that compose the medication, such as polysorbate, used to increase drug solubility.[15] Some authors suggested that pre-existing or recently developed antibodies against omalizumab could be responsible for the reactions. However, a post-marketing pharmacosurveillance using a new method to detect IgE antibodies for omalizumab did not show an apparent correlation between anaphylaxis or reactivity in the skin test or presence of antibodies of IgE isotype to omalizumab.[16]

Clinical studies, as well as real-life studies with the pediatric population, demonstrated an acceptable

overall safety profile. The more frequent adverse reactions were nasopharyngitis, headache, fever, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis. A previously published meta-analysis of three randomized controlled studies revealed that frequency of adverse events was similar between omalizumab (76.3%) and placebo (74.2%), as well as the frequency of serious adverse events (5.2 and 5.6%, respectively). There was no evidence of increased risk for anaphylaxis, urticaria, hypersensitivity reactions, or malignant diseases.[16,17]

A clinical trial of omalizumab for chronic spontaneous urticaria included more than 1,000 patients and did not observe any death or significant serious adverse event related to the medication. The most common adverse events after subcutaneous administration were injection-site reactions, followed by upper respiratory tract infection and headache.[18]

In 2018, a meta-analysis of 67 real-life studies on the efficacy of omalizumab found an average adverse event rate of 4% (1-7%) vs. 2.9-8% in clinical trials.[19]

In replicated studies, POLYP1 and POLYP2, on the use of omalizumab in CRSwNP, 50.4% of patients developed at least one adverse event. Most events in both studies ranged from mild to moderate intensity, and the most common ones were headache, nasopharyngitis, and injection-site reactions. Three serious cases were reported in patients using omalizumab (2.2% [1 case of snake bite, 1 hand fracture, and 1 case of asthma exacerbation/ worsening]).[20]

Mepolizumab

Mepolizumab is a humanized IgG1 monoclonal antibody that directly targets IL-5. Thus, it prevent the attachment of this cytokine to IL-5 receptor alpha chains in eosinophils and basophils, leading to a decrease in the number of eosinophils and, thus, in eosinophilic airway inflammation.[21] Mepolizumab is approved for the treatment of severe asthma in children over 6 years of age (40 mg/4 weeks), adolescents (≥ 12 years), and adults (100 mg/4 weeks).[22]

The adverse reactions associated with the use of mepolizumab described in clinical trials were headache in 29% of patients, asthma worsening in 27%, bronchitis in 21%, and injection-site reactions in 12%. Two individuals developed severe Herpes zoster, and for this reason, the US Food & Drug Administration recommends vaccinating patients older than 50 years with indication for using this drug. Recently, in a retrospective study on anaphylaxis related to immunobiological agents used to enhance type 2 response, Li et al. identified 102 cases caused by mepolizumab. Sixty-nine patients received mepolizumab for the treatment of severe asthma, 1 for chronic eosinophilic pneumonia, and 32 had unknown indication. Of the 102 cases, 2 (2%) resulted in death, and 31 (30%) required hospitalization.[21,23-25]

Mepolizumab showed to be well tolerated in the pediatric population. However, there was the report of a case of histiocytic necrotizing lymphadenitis and another case of varicella infection after exposure to mepolizumab, both in 12-year-old patients.[26,27]

Benralizumab

Benralizumab was the second anti-IL-5 agent approved in Brazil for severe eosinophilic asthma in patients 18 years and older. It is a humanized monoclonal antibody (IgG1κ) that targets the IL-5 receptor alpha subunit, resulting in eosinophil and basophil apoptosis via antibody-dependent cytotoxicity and decreased formation of these cells.[28]

It is subcutaneously administered at a dose of 30 mg every 4 weeks in the first 3 doses and then every 8 weeks.[21,29]

In clinical trials, the percentage of patients who had an adverse event with benralizumab ranged from 65% to 75%. The most commonly reported adverse events were nasopharyngitis (12-21%) and asthma worsening (11-13%). Hypersensitivity reactions (anaphylaxis, angioedema, urticaria) occurred in approximately 3% of individuals. Li et al. found 63 reported cases of anaphylaxis by benralizumab, with a risk for prolonged hospitalization higher than that of other immunobiological agents, with reports of requirement for hospitalization in 27 (42.86%) patients. For other biological agents, the proportion was the following: omalizumab (28.92%), mepolizumab (29.81%), and dupilumab (40.32%).[25,30]

A multicenter phase 3 extension study included patients from pivotal trials, SIROCCO and CALIMA, who received benralizumab 30 mg every 4 or 8 weeks, in addition to those who had received placebo in these studies. The latter patients were re-randomized in a 1:1 ratio, to receive benralizumab 30 mg every 4 or 8 weeks. In this two-year study, named BORA, the

most common serious adverse events were asthma exacerbation (3-4%) and pneumonia (< 1 to 1%).[31]

Despite concerns with the risk of suppression of anthelmintic immunity by immunobiological drugs targeted at IL-5, so far there is no report of cases that developed parasitic infections during or after trials of such products.[32] However, we consider it advisable to perform an investigation for helminthic infestation in patients with indication for anti-IL-5 biological agents.

Dupilumab

Dupilumab is the first fully human immunobiological agent developed for allergic diseases and targets the IL-4 alpha receptor, which inhibits IL-4 and IL-13 signaling.[21] This monoclonal antibody was approved for moderate-to-severe DA (children ≥ 6 years, adolescents, and adults), severe eosinophilic asthma (≥ 6 years), and CRSwNP (≥ 18 years). The dose is variable, depending on indication.[3]

In a 52-week phase 3 study involving 1,902 asthmatic patients, including adolescents and adults, dupilumab showed a good safety profile.

The most common reactions, compared with placebo, were injection-site reaction (14-18% vs. 6%), oropharyngeal pain (2% vs. 1%), and eosinophilia (4.1% vs. 0.6%).[34] Another study observed eosinophilia in up to 14% vs. 1% with placebo.[35] Transient eosinophilia may reach ≥ 3,000 cells/μL and is believed to result from inhibition of migration of these cells to tissues.[32,34] The consequences of this hypereosinophilia were rare: two patients presented with eosinophilic pneumonia, in addition to another two patients with vasculitis compatible with eosinophilic granulomatosis with polyangiitis.[30] Currently, there are no recommendations on monitoring of eosinophilia in patients using dupilumab.

Dupilumab was assessed in children with severe asthma and aged from 6 to 11 years. The frequency of adverse events during the 52 weeks of the study was similar between test and placebo groups. Serious adverse events were reported in 13 patients (4.8%) in the dupilumab group and in 6 (4.5%) in the placebo group. Eosinophilia occurred in 5.9% and 0.7% of the patients in the dupilumab and placebo group, respectively. Most episodes of eosinophilia were self-limited laboratory findings without any associated symptoms. The frequency of conjunctivitis was low in both groups; one case of keratitis was reported in each group.[36]

The pathogenesis of conjunctivitis associated with dupilumab is still not totally elucidated. An association between pre-existing ocular diseases related to AD may be responsible for the increased incidence of conjunctivitis in patients treated with dupilumab, but it was not identified in studies on other type 2 diseases. A possible explanation would be an increase in expression of IFNγ, the Th1 cytokine, which would cause secretory dysfunction and loss of conjunctival goblet cells, worsened by IL-13 inhibition due to dupilumab.[37]

Other ocular complications occurred in 1-10% of patients in the form of blepharitis, ocular pruritus, keratitis, and dry eye. Orofacial herpes simplex infection was also reported in 1-10% of patients. Hypersensitivity reactions, especially generalized urticaria, occurred in 0.1-1%. Much rarely, there was the development of serum sickness (< 0.01%).[30]

As for anaphylaxis, a recently published study identified 62 patients who developed anaphylaxis due to dupilumab, most of which used this drug for AD (23; 37%) and severe asthma (19; 30.6%). The others received dupilumab for the following indications: 2 (3.2%) for aspirin-exacerbated respiratory disease; 1 (1.6%) for CRSwNP; and 1 (1.6%) for unknown indication.[25]

In phase 3 trials with dupilumab for CRSwNP, adverse events were rare. In the trial that lasted for 24 weeks, LIBERTY NP SINUS-24, the more common events were nasopharyngitis, CRSwNP worsening, headache, asthma worsening, epistaxis, and injection-site erythema. In the LIBERTY NP SINUS-52 trial, which assessed use of dupilumab for 52 weeks, the most frequent adverse events were cough, bronchitis, arthralgia, accidental overdose, and injection-site reactions.[38]

Recently, a systematic review was conducted to evaluate the association between use of dupilumab and development or worsening of psoriasis symptoms. Twenty-six studies with 47 patients met the review inclusion criteria. All patients were adults (age range, 24-92 years), and most of them (43; 91%) were given dupilumab for AD. The remaining patients were given dupilumab for asthma (1), alopecia areata (1), and other dermatitis (2). The interval from initiation of dupilumab to development/worsening of psoriasis was 3.7 months. Psoriasis led to cessation of dupilumab in 16 of the 33 patients (48%) for which cessation vs. continuation was reported. The accurate immunological mechanism through which dupilumab induces the development of psoriasis in certain

patients remains unknown. This is believed to be due to the fact that IL-4 levels were high in AD, and that this cytokine downregulates T-helper 1 and T-helper 17 lymphocytes, both of which are increased in patients with psoriasis. Dupilumab may prevent this inhibition by blocking IL-4 signaling, which promotes the occurrence of psoriatic inflammation. This explanation is consistent with the already known observation that coexistence of psoriasis and AD in the same patient is less common than expected based on the prevalence of the two diseases.[39]

Close remarks

Increased prevalence of asthma and allergic diseases resulted in the need for investigations on new treatments to better control symptoms, improve quality of life, and reduce serious crises and hospitalizations. Advances in knowledge on pathogenic mechanisms allowed for identification of different endotypes and phenotypes, as well as new therapeutic targets involved in allergic inflammation. Availability of effective immunobiological agents to control these diseases is extremely important, but patient safety is always the primary goal.

The main adverse events of immunobiological agents that act on type 2 response are mostly mild, such as injection-site reaction, respiratory tract infection, and headache. The mechanisms of action of these immunobiological agents have low potential for immunosuppression, with good safety profiles with regard to infections. We emphasize frequency or severity of respiratory tract infection, including SARS- CoV-2, are not statistically higher, compared to placebo, in subjects using immunobiological agents described here.

A small risk for anaphylaxis has also been described; thus, we highlight the importance of using these medications in day-hospitals, with medical supervision.

In the future, the development of biomarkers can help prevent the risk for adverse events, especially immediate reactions, for which protocols of investigation and desensitization need to be improved and standardized. Therefore, it is important to perform clinical and laboratory monitoring of adverse events (e.g., eosinopenia or eosinophilia).

Finally, it is worth highlighting that the use of immunosuppressive agents, occasionally used in the treatment of allergic diseases, is associated with adverse events. With the development of precision medicine, immunobiological agents have been increasingly incorporated into the practice of allergists and immunologists. These drugs cause hypersensitivity reactions, but, fortunately, most of them have low severity.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Evolutionary aspects of immunopathological phenomena with emphasis on COVID-19

Aspectos evolutivos dos fenômenos imunopatológicos com ênfase na COVID-19

Selma Giorgio[1], Pedro Henrique Gallo-Francisco[1]

ABSTRACT

Natural selection is the main mechanism by which species evolve, and it favors phenotypes associated with an effective immune defense against pathogens. However, human immune responses and the occurrence of immunopathological phenomena vary considerably from individual to individual. Infection with SARS-CoV-2, a virus of the *Coronaviridae* family causing the disease known as COVID-19, induces exacerbated inflammatory immune responses and cytokine storm in severe cases. In this review, we discuss, in the light of Evolution, this apparent paradox between the immune responses and the 3 main factors contributing to the maintenance of hyperactive phenotypes: the cost-effectiveness of immune responses, coevolution, and the life history of the species.

Keywords: SARS-CoV-2, cytokines, biological evolution.

RESUMO

A seleção natural é o principal mecanismo da evolução das espécies, e favorece fenótipos com defesas imunes efetivas contra patógenos. Entretanto, há uma grande variação das respostas imunes entre os indivíduos da espécie humana e a ocorrência de fenômenos imunopatológicos. A infecção com o vírus da família *Coronaviridae*, SARS-CoV-2, responsável pela doença conhecida como COVID-19, induz a respostas imunes inflamatórias exacerbadas e à tempestade de citocinas, nos casos graves. Nesta revisão discutiremos, à luz da Evolução, esse aparente paradoxo entre as respostas imunes, e os três principais fatores que contribuem para a manutenção dos fenótipos hiperativos: o custo-benefício das respostas imunes, a coevolução e a história de vida da espécie.

Descritores: SARS-CoV-2, citocinas, evolução biológica.

Introduction

The 1st International Symposium of Immunopathology, held in 1958, gathered for the first time researchers interested in the impact of immunology on medical practice. After this symposium, immunopathology was defined as the study field on immune reactions that cause, modify, or follow pathological states.[1] In a teaching monography published in 1978 by the *American Journal of Pathology*,[2] Stewart Sell called attention to the ambiguity of the word immunopathology, composed of two terms with different meanings: immunity, which refers to protective immune responses against external agents, and pathology, which is the study of diseases.[2] Pathological conditions such autoimmune diseases, hypersensitivity, and allergies to innocuous substances or foods, and pathogen-induced immunopathological phenomena result from inappropriate immune responses. Optimal immune response results in pathogen elimination and reestablishment of organism's homeostasis without causing cell and tissue damage.[3,4]

There is an apparent paradox in the immune system of the human species, because natural selection, the main mechanism of Evolution, should select phenotypes with effective immune defenses against pathogens; however, human immune

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responses and the occurrence of immunopathological phenomena vary considerably from individual to individual.[4,5] Infection with SARS-CoV-2, a virus of the *Coronaviridae* family, responsible for the disease known as coronavirus disease (COVID-19) and for the pandemic experienced recently,[6,7] is one example of this paradox. Mortality rates from this disease are approximately 3.7%, reaching 50% in critically ill patients.[8] The main symptoms associated with COVID-19 are fever (98% of patients), cough (76%), dyspnea (55%), and myalgia or fatigue (44%). Severe disease is characterized by pneumonia and severe acute respiratory syndrome (SARS).[8]

The SARS-CoV-2 virus colonizes upper airways and the nasopharyngeal cavity.[9] The innate immune system is involved in initial response to infections, with the participation of Toll-like receptor (TLR)-3, TLR-4 and TLR-7, which bind the following viral molecules, present in the cytoplasm of the infected epithelial cells: dsRNA, Spike protein, and ssRNA, respectively, resulting in the production of various cytokines with antiviral effects, such as interferons (IFNs) and interleukin-6 (IL-6), an inflammatory cytokine (Figure 1). Adaptive immune response, which is critical for viral clearance, has the participation of T CD4, T CD8, and B lymphocytes and antibodies.[8,9] With the migration of the dendritic cells that internalized viral antigens to regional lymph nodes, there is activation of T lymphocytes (Figure 1). These proliferate and migrate to the lung, inducing local cytokine production and cell recruitment.[8,9] However, antiviral immunological responses may result in immunopathology, when high levels of inflammatory cytokines and chemokines, such as IL-1β, IL-6, IL-8, IL-12, tumor necrotizing factor (TNF-α), and IFNs are systematically produced in the lung, leading to increased immune activation and inflammation and creating a positive feedback loop, which results in extensive tissue lysis and loss of organ function (Figure 1).[8-10]

Although the severity of clinical manifestations of COVID-19 is related to systemic conditions manifested in infected individuals,[6] the intensity and reactivity

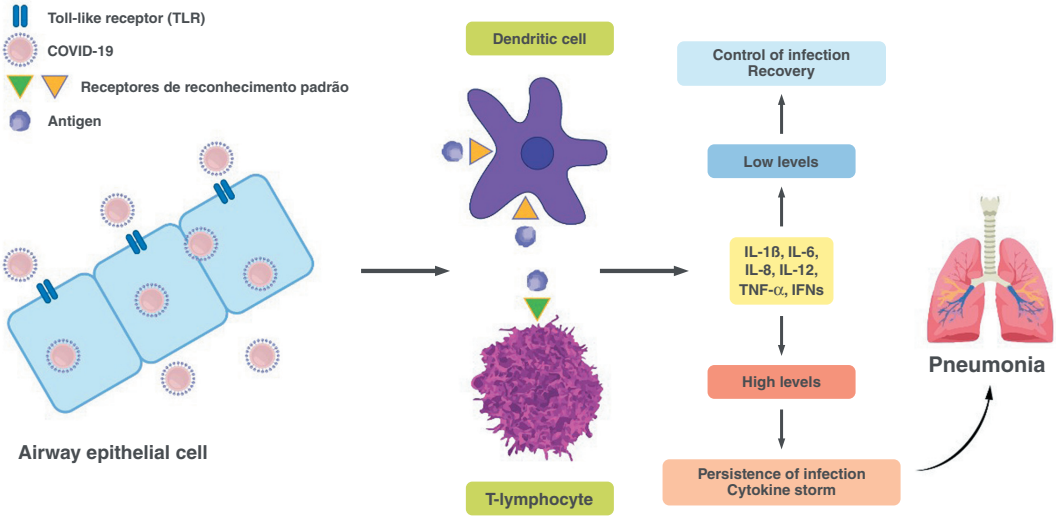

Figure 1
Schematic representation of immune responses against the SARS-CoV-2 virus

The virus interacts with Toll-like receptors (TLR) in airway epithelial cells, inducing the production of cytokines. Dendritic cells transporting viral antigens migrate to regional lymph nodes, present these antigens, and activate T lymphocytes, which migrate to the lungs. Individuals may exhibit different immune response profiles: one leading to the production of controlled levels of inflammatory cytokines, which results in viral clearance and recovery of the infected individual; and another leading to the production of very high levels of inflammatory cytokines, which causes persistence of viral infection and pneumonia

of immune responses, and consequently disease outcomes, vary among infected individuals. Uncontrolled inflammation, known as hyperinflammatory syndrome or cytokine storm, is directly associated with mortality and results in SARS.[8] This review aims to discuss, in the light of Evolution, the following question: why are exacerbated immune responses, such as uncontrolled production of inflammatory cytokines, observed in COVID-19 and also in septic shock and malaria,[13] maintained in the population?

In Evolutionary Medicine, the theory of Evolution is applied to the understanding of health problems and improvement of medical approaches.[14] Initially, one may consider that immunopathological phenomena conflict with Darwinism and Evolution,[4,12] because natural selection operates in the immune system to optimize it and maintain the phenotype most adapted to the environment where an organism lives.[4,5,11] However, natural selection also favors "defective" immune responses, which result in immunopathological phenomena, i.e., in phenotypes with propensity to excessive inflammatory responses. The three main factors that contribute to the maintenance of phenotypes with hyper-reactive responses are: cost-effectiveness, coevolution, and the life history of the species.[4,5,11,12] In this review, we discuss these factors and answer the aforementioned question.

Data sources

A non-systematic literature review was performed, with search and selection of articles available in the PubMed, SciELO, Web of Science, and Google Scholar System databases and published from 1957 to 2022, in English or Portuguese, with no location restrictions, using the following words: "SARS-CoV-2", "COVID-19", "immunopathology", "inflammation", "cytokines" or "Biologic Evolution". The literature search was conducted in January 2022.

Cost-effectiveness

Although fine adjustments of immune reactions to stressful situations occur frequently, the intensity of immune responses varies considerably from individual to individual, ranging from sterile protective responses to hyper-inflammation, a fact that can be explained by trade-off.[5,15,16] The concept of trade-off refers to selective conflicts in which a species, by following an advantageous evolutionary pathway, "will pay a price" for it, i.e., there will be some disadvantages associated with this biological innovation.[5,17,18] For example, the costs for complete viral clearance are tissue damages caused by immune system cells when combating the pathogen.[5] Mathematical models of several situations related to infections[5,19,20,21] indicate that the risk of death due to infections with virus species that has a transmission pattern similar to that of SARS-CoV-2 is higher than the risk of death due to immunopathological phenomena resulting from immune responses. Natural selection will favor more reactive and intense immune defenses, even with some risk of death to the host.[5,22] However, there are two additional costs: the possibility of errors in antigen recognition (self-recognition, causing autoimmune diseases) and collateral damage exacerbated in the infected tissue.[5,20-23]

A meta-analysis of 86 studies of cytokine gene knockout mice showed that the risk of death due to infection is higher than that due to immunopathological phenomena.[24] For example, animals IL-10$^{-/-}$, i.e., which did not produce this anti-inflammatory cytokine, infected with the murine cytomegalovirus showed a decrease in immunopathological effects in the liver, whereas viral replication and mortality rates increased.[26] Therefore, increased viral load was directly associated with increased mortality in these animals. In evolutionary terms, the persistence of immunopathological phenomena and their possible cost exist because immunological response (protection) brings immediate benefits, such as pathogen elimination.[24]

Coevolution

Another factor that contributes to the persistence of intense immune responses in individuals of the human species is coevolution, and this section is intended to make a brief description of this contribution. The immune system results from the simultaneous evolution (coevolution) of hosts, pathogens, and symbionts.[4,5,11,22]

So far, the human species has two important epidemiological transitions.[27] The first one happened in the Paleolithic period (10,000 BC), in which hunters/gatherers lived in small groups and were nomads, having contact with helminths, saprophytic bacteria, *Salmonella*, and *Toxoplasma*.[27] After the Neolithic period (3,300 BC), they started to live in highly populated settlements and together with farm animals, in frequent contact with feces, mud,

untreated water, and organisms transmitted via the fecal-oral route, such as helminths, as well as *Mycobacterium tuberculosis*, and the bacteria causing typhus and cholera.[27,28] The second epidemiological transmission, in turn, occurred later, in the 1800s, when the human species progressively starts to live in large urban agglomerations, with access to treated water and hygiene habits, thus interacting less with farm animals, in addition to using anthelmintics and antibiotics and to consuming industrialized food.[27,28] The consequence of these changes was reduced contact with helminths and pseudocommensal bacteria, known as "old friends", present in mud and untreated water, which results in a more homogeneous intestinal microbiota.[27,28]

With reduced exposure to various pathogens and symbionts (old friends), the microenvironment of the immune system has also changed, and consequently, its regulatory profile, which became less inflammatory. This is the case of helminths, which developed very competent immune regulatory mechanisms during coevolution with their hosts.[29] For example, *Brugia malayi* has molecules that mimic the macrophage-migration inhibition factor (MIF) and transforming growth factor-beta (TGF-β) cytokines, which, among various functions, are anti-inflammatory.[27-29] *Schistosoma mansoni*, an intestinal parasite, produces phosphatidylserine, phosphorylcholine, and various glycans, which interact with dendritic cells and activate TH2 and regulatory lymphocytes in their hosts. Onchocystatin, from *Onchocerca volvulus*, prevents the activation of T-lymphocytes and increases the production of anti-inflammatory cytokines.[29] These strategies adopted by helminth parasites result in regulatory and less inflammatory immune responses, thus facilitating their survival for a prolonged time in their hosts and, consequently, leading to the chronic infections observed in helminthiasis. Furthermore, this contributed to the presence of a less reactive and less inflammatory immunological profile in the host population.[27-29]

As previously seen, natural selection favors hosts that develop reactive and intense immune responses, and the main coevolutionary legacy of "old friends" was the modulation of these immune responses. With the loss of "old friends," i.e., reduced contact with parasites and symbionts, immune regulations cease to occur, and the more reactive and inflammatory immunological profile prevails in the population. Indeed, epidemiological data indicate a high incidence of chronic diseases with inflammatory profile, such as diabetes, asthma, and autoimmune diseases in the urban populations of industrialized countries.[27,28]

Other factors involved in the onset/maintenance of the "inflammatory" phenotype in urban populations are the prevalence of obesity, a condition characterized by increased levels of inflammatory cytokines; deficiency of vitamin D, a molecule involved in immune regulation, due to lack of sun exposure; and contact with pollutants such as dioxin, which activates inflammatory TH17 lymphocytes.[27,28,30]

Life history

The life history of a biological species is characterized by aspects that directly affect its reproductive success, such as anatomy, reproductive lifespan, size of the offspring, parental investment, maturation time, life expectancy, and behavior.[5,16,31] Reproductive and survival processes through which organisms of a given species complete their life cycle, as well as the energy allocated in each phase of their development, define the aspects of each stage of life. Limitation of environmental resources imposes trade-offs and restrictions and, thus, no individual can develop, reproduce rapidly, and invest on longevity at the same time.[5,11,16,31] It is necessary to prioritize a set of traits/functions to which energy will be allocated in each phase of organism's life.[31] Furthermore, life history explains why species have different patterns of reproduction, development, and longevity, which are determined by the allocation of resources to maximize reproductive success. The events that occur during the life of an organism are also shaped by demographic aspects.[31] Human beings are characterized by long lives, few offspring, and a long post-natal phase of nutritional dependency, with high parental investment. There is also a strong selective pressure in the early stage of species development, because the adaptive cost of juvenile mortality is higher than that of the mortality of older individuals, who do not reproduce anymore.[22,30,31] Therefore, the early stage of development should privilege a very reactive immune system, with memory and plasticity, which is indeed observed in our species. The genes involved in reactive and intense immune responses, which combat pathogens and benefit individuals in the early years of life, may be detrimental in the maturity stage, because these genes induce immunopathological phenomena.[5,19,23,32,33] The genetic traits selected in the early life development may have negative effects in other stages.

More empirical, experimental and theoretical investigations are needed; however, studies have undoubtedly advanced in the definition of evolutionary and adaptive aspects that result in the immunopathological phenomena experienced by the human species.

Conclusions

In this brief review, we assessed, in the light of Evolution, the apparent paradox of immune responses in the human species, immune reactions that should control infections, but that can result in irreversible immunopathological damages (e.g., cytokine storm, which occurs in severe cases of COVID-19). There is the understanding that the cost-effectiveness of exacerbated immune responses partially explains the maintenance of this trait during evolution: the risks of death due to infections exert a higher selective pressure than the risks of death due to immunopathological phenomena.

Coevolution of pathogens, symbionts, and hosts contributed to the emergence of immune regulatory responses, and epidemiological transitions of the human species contributed to the emergence of less immunoregulatory and more inflammatory phenotypes. Furthermore, the life history of our species reveals how demographic contexts and resource allocation are determining factors for the maintenance of a more reactive immune system. Additionally, knowledge on the evolutionary bases of immune response variability will help reinterpret immunopathological phenomena and formulate additional prevention and treatment strategies.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

JAK inhibitors in the treatment of atopic dermatitis

Inibidores de JAK no tratamento da dermatite atópica

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ABSTRACT

Atopic dermatitis is the most common inflammatory skin disease worldwide. The JAK/STAT pathway plays an important role in the disease mechanism, and small-molecule JAK inhibitors are drugs with great potential for use in atopic dermatitis. We systematically reviewed PubMed using the search terms "atopic dermatitis" AND/OR "JAK inhibitors" AND/OR "small molecules" for studies published between 2017 and 2022. Results from phase III trials evaluating both topical and systemic application of JAK inhibitors were included. Of 646 studies retrieved, 37 evaluating the efficacy and safety of JAK inhibitors in humans were selected for analysis. When properly indicated, the use of JAK inhibitors yielded positive results, some of which were superior to those of recommended treatments for the control of atopic dermatitis, with a good safety profile.

Keywords: Atopic dermatitis, JAK inhibitors, small molecules.

RESUMO

A dermatite atópica é a doença inflamatória cutânea mais prevalente mundialmente. A via JAK/STAT tem papel importante no mecanismo da doença e as pequenas moléculas inibidores de JAK são fármacos com grande potencial de uso na dermatite atópica. Foi realizada uma revisão sistemática da literatura na base de dados PubMed, utilizando os termos "atopic dermatitis" e/ou "JAK inhibitors" e/ou "small molecules" entre 2017 e 2022. Foram incluídos os resultados disponíveis de estudos de fase 3, avaliando o uso de inibidores de JAK em apresentações tópicas e sistêmicas. Entre 646 estudos, foram selecionados 37 em humanos que avaliaram a eficácia e segurança dos inibidores de JAK. Os resultados do uso, quando bem indicados, mostraram-se positivos e em alguns casos superiores a outros tratamentos já preconizados para o controle da dermatite atópica, com um bom perfil de segurança.

Descritores: Dermatite atópica, inibidores de JAK, pequenas moléculas.

Introduction

Atopic dermatitis, a chronic, recurrent inflammatory disease also known as atopic eczema, is the most prevalent inflammatory skin disease. Furthermore, recent evidence reveals that it is among the top 30 chronic diseases with the highest non-fatal burden of disease, or years lived with disease (YLD), worldwide.[1,2]

It is characterized by pruritus and eczema, and its morphology are seen in different anatomical locations that may vary depending on the age of the patient, and is manifested with a broad spectrum of clinical presentations. Considering its clinical heterogeneity, epidemiological data on its prevalence are variable.

The International Study of Asthma and Allergies in Childhood (ISAAC) was a study designed to estimate the prevalence of allergic diseases among children and adolescents in different regions of the world. In the first phase, children aged 6 to 7 years and adolescents

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aged 13 to 14 years from 56 and 38 countries, respectively, answered a standardized questionnaire. The results for the prevalence of atopic dermatitis varied between 0.3% and 20.5%, depending on the geographical region, and the disease showed to be more prevalent in regions of lower latitude and with smaller temperature variations. In Brazil, the mean prevalence of eczema was 11.5% among participants of 20 Brazilian cities, assessed from 2002 to 2003.[3]

Disease pathophysiology is well understood. Atopic dermatitis is caused by genetic factors, changes in immunological and inflammatory response, and changes in skin barrier. Patients with atopic dermatitis present an exacerbated type 2 immunological response. Type 2 inflammatory cytokines, especially interleukin (IL)-4, IL-5 and IL-13, can inhibit proteins and lipids in the skin barrier, contributing to its disruption. Furthermore, it is known that these type 2 cytokines participate also in the activation of eosinophils and mast cells, in addition to increasing the production of IgE.[4]

Janus kinase (JAK) enzymes are important mediators of the intracellular action of several substances, including inflammatory cytokines. When their receptors are activated, there is phosphorylation of signal transducers and activators of transcription (STATs), which may be translocated to the cell nucleus, inducing transcription and regulation of expression of the selected genes. This pathway stimulates the expression of several molecules and cytokines that facilitate leukocyte mobilization and cell proliferation. Therefore, the JAK/STAT pathway has a crucial role in the function of hematopoietic and immunological cells, and recent studies show that this pathway may have higher susceptibility to activation in patients with asthma, atopic dermatitis, and allergic rhinitis, diseases characterized by increased type 2 inflammatory interleukins[5,6] (Figure 1).

Patients with moderate-to-severe atopic dermatitis who did not respond to topical treatments require systemic immunosuppressant drugs. With improved understanding on disease pathophysiology, the use of immunobiological agents was approved for atopic dermatitis. Dupilumab is the only agent approved for the treatment of atopic dermatitis.[7,8] It was considered a hallmark in the direction that disease treatment could take. It is a monoclonal IgG4 antibody that inhibits IL-4 receptor and IL-13 in type 2 inflammatory response.[9] It is a well-tolerated medication with a good response in groups of adults and children over 6 years of age. Despite promising results, there is a group of patients who did not respond to treatment, either partially or totally, reinforcing the need to continue scientific studies for the development of new therapeutic classes.

JAK inhibitors are small molecules, i.e., low-molecular-weight drugs, which can easily pass through the cell membrane and reach intracellular targets. Thus, they act inhibiting signaling mediated by specific cytokines, acting in chains of specific receptors of Janus Kinase subtypes (JAK-1, JAK-2, JAK-3) and/or Tyrosine-Kinase 2 (TYK-2).[10,11] The first JAK-inhibitor drug was approved for clinical practice in 2011, for autoimmune disease.[12] Its clinical use is comprehensive, ranging from oncology up to combat of viral diseases, and shows great potential of action in allergic diseases with type 2 immunological response. Future perspectives of JAK inhibitors have been increasingly assessed in atopic dermatitis, and its use have been recently regulated in several countries, both in topical and systemic forms.

Methodology

A systematic literature review was conducted, using the PubMed/MEDLINE database as the research source. The terms “atopic dermatitis” and/or “JAK inhibitors” and/or “small molecules” were used, from 2017 to July 2022. The choice for this date was based on the fact that 2017 was the year when dupilumab was approved for use in atopic dermatitis both by the FDA and by ANVISA, being the first biological drug approved.

This review selected clinical trials on atopic dermatitis in humans treated with systemic or topical JAK inhibitors that assessed drug efficacy and safety.

The selection excluded studies characterized as literature reviews, case reports, expert opinions, laboratory or animal experimental studies, studies focusing only on drug pharmacokinetics, and studies that assessed the use of JAK inhibitors in other diseases.

Results

A total of 646 studies were found, of which 609 were excluded because they were literature reviews, laboratory or animal experimental studies, duplicate results, or because they did not meet the other inclusion criteria. Thirty-seven publications showing the results

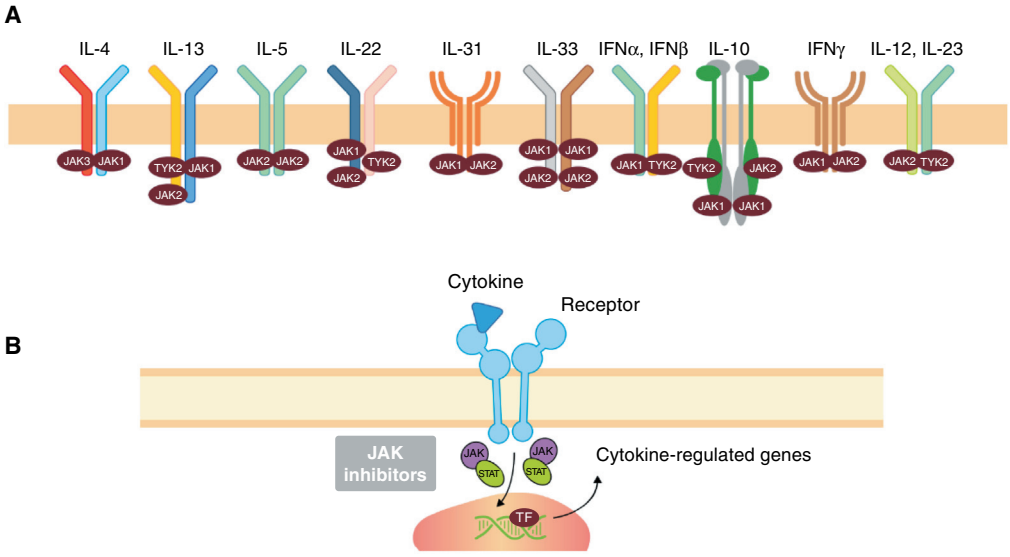

Figure 1
A) JAK signaling with cytokines involved in immunological response and immune-mediated diseases
B) JAK/STAT pathway
Adapted from Ahn J, et al.[56]

of clinical trials involving JAK inhibitors were selected. Considering that some publications display different points of analysis based on the same population, i.e., they are derived from the same controlled trial, it was observed that the 37 selected articles were based on 25 clinical multicenter randomized trials.

The selected articles analyzed the effects of different drug doses, compared with a placebo group and in some cases with other treatments already established in the literature. The main scores used to assess disease evolution were the Eczema Score and Severity Index (EASI) and the Investigator Global Assessment (IGA). The EASI score consists of rater's assessment to define the extent of the lesion in each body region and then the severity of erythema, edema, excoriation, and lichenification is classified from 0 to 3. The sum of the points classifies disease severity, with a score above 21 points indicating severe disease. Previous studies assessed the EASI scores of patients before treatment and improvement in percentage after using the medications. One of the outcomes assessed was the proportion of patients who showed 75% improvement from baseline, named EASI-75, or 90% clinical improvement, EASI-90, for example. The IGA, in turn, consists of the morphological description of lesions, ranging from 0 to 4. Most studies established an IGA score of 0/1 (asymptomatic or mild disease) as a therapeutic target.

In addition to also using other scales to assess control of lesions and quality of life, some studies assessed the severity of patients' pruritus through the Pruritus Numerical Rating Scale (NRS), which consists of two questions scored from 0-10. Significant improvement was considered when patients showed a decrease of 4 points or more in the NRS scale.

The main results of phase 3 studies found when applying the search terms on PubMed, considering systemic and topical drugs, are shown in Table 1.

Table 1
Phase 3 studies with JAK inhibitors in atopic dermatitis

Drug	Target	Phase 3 study	Inclusion criteria	Population	Time of assessment	EASI-75	IgA 0/1 (Improvement ≥ 2 points)	Most common adverse effects
Upadacitinib (Up.) Oral route	JAK-1	MEASURE UP 1 (NCT03569293)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	847 (12 - 75 years)	16 weeks	Up. 15 mg: 69.6% Up. 30 mg: 79.7% Placebo: 16.3%	Up. 15 mg: 48.1% Up. 30 mg: 62.0% Placebo: 8.4%	Acne, URTI, nasopharyngitis, headache, increased CPK
		MEASURE UP 2 (NCT03607422)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	836 (12 - 75 years)	16 weeks	Up. 15 mg: 60.1% Up. 30 mg: 72.9% Placebo: 13.3%	Up. 15 mg: 38.8% Up. 30 mg: 52.0% Placebo: 4.7%	Acne, URTI, nasopharyngitis, headache, increased CPK
		AD UP (NCT03568318)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	901 (12 - 75 years)	16 weeks	Up. 15 mg: 64.6% Up. 30 mg: 77.1% Placebo: 26.4%	Up. 15 mg: 39.6% Up. 30 mg: 58.6% Placebo: 10.9%	Acne, nasopharyngitis, URTI, herpes oral, increased CPK, headache
		HEADS UP (NCT03738397)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4	692 (18 - 75 years)	16 weeks	Up. 30 mg: 71.0% Dup. 300 mg: 61.1%	Not reported	Acne, URTI, increased CPK, nasopharyngitis
Abrocitinib (Ab.) Oral route	JAK-1	JADE MONO-1 (NCT03349060)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	387 (12 - 75 years)	12 weeks	Ab. 100 mg: 39.7% Ab. 200 mg: 62.7% Placebo: 11.8%	Ab. 100 mg: 23.7% Ab. 200 mg: 43.8% Placebo: 7.9%	Nausea, nasopharyngitis, headache, URTI
		JADE MONO-2 (NCT03575871)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	391 (12 - 75 years)	12 weeks	Ab. 100 mg: 44.5% Ab. 200 mg: 61.0% Placebo: 10.4%	Ab. 100 mg: 38.1% Ab. 200 mg: 28.4% Placebo: 9.1%	URTI, nasopharyngitis, headache, nausea, vomiting, acne
		JADE COMPARE (NCT03720470)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	837 (≥ 18 years)	12 weeks	Ab. 100 mg: 58.7% Ab. 200 mg: 70.3% Dup. 300 mg: 58.1% Placebo: 27.1%	Ab. 100 mg: 36.6% Ab. 200 mg: 48.4% Dup. 300 mg: 36.5%	Similar to the previous studies
		JADE TEEN (NCT03796676)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	285 (12 - 17 years)	12 weeks	Ab. 100 mg: 68.5% Ab. 200 mg: 72.0% Dup. 300 mg: 41.5%	Placebo: 14.0% Ab. 100 mg: 41.6% Ab. 200 mg: 46.2%	URTI, headache, nasopharyngitis, dizziness, acne, vomiting

Table 1 *(continuation)*
Phase 3 studies with JAK inhibitors in atopic dermatitis

Drug	Target	Phase 3 study	Inclusion criteria	Population	Time of assessment	EASI-75	IgA 0/1 (Improvement ≥ 2 points)	Most common adverse effects
Baricitinib (Bar.) Oral route	JAK-1 JAK-2	BREEZE 1 (NCT03334396)	EASI ≥ 16 IGA ≥ 3	624 (≥ 18 years)	16 weeks	Bar. 1 mg: 17.3% Bar. 2 mg: 18.7% Bar. 4 mg: 24.8% Placebo: 8.8%	Bar. 1 mg: 11.8% Bar. 2 mg: 11.4% Bar. 4 mg: 16.8% Placebo: 4.8%	Nasopharyngitis, URTI, diarreia, headache
		BREEZE 2 (NCT03334422)	EASI ≥ 16 IGA ≥ 3	615 (≥ 18 years)	16 weeks	Bar. 1 mg: 12.8% Bar. 2 mg: 17.9% Bar. 4 mg: 21.1% Placebo: 6.1%	Bar. 1 mg: 8.8% Bar. 2 mg: 10.6% Bar. 4 mg: 13.8% Placebo: 4.5%	Herpes simplex, nasopharyngitis, increased CPK, headache
		BREEZE 4 (NCT03428100)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10% Contraindication to ciclosporin	463 (≥ 18 years)	16 weeks	Bar. 1 mg: 22.6% Bar. 2 mg: 27.6% Bar. 4 mg: 31.5% Placebo: 17.2%	Bar. 1 mg: 12.9% Bar. 2 mg: 15.1% Bar. 4 mg: 21.7% Placebo: 9.7%	Nasopharyngitis, herpes simplex, influenza, headache, back and abdominal pain, diarrhea, conjunctivitis
		BREEZE 5 (NCT03435081)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10%	440 (≥ 18 years)	16 weeks	Bar. 1 mg: 12.9% Bar. 2 mg: 29.5% Placebo: 8.2%	Bar. 1 mg: 12.9% Bar. 2 mg: 24.0% Placebo: 5.4%	Nasopharyngitis, URTI
		BREEZE 7 (NCT03733301)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10%	329 (≥ 18 years)	16 weeks	Bar. 2 mg: 43.1% Bar. 4 mg: 47.7% Placebo: 22.9%	Bar. 2 mg: 23.9% Bar. 4 mg: 30.6% Placebo: 14.7%	Folliculitis, URTI, nasopharyngitis
Ruloxitinib (Rul.) Topic	JAK-1 JAK-2	TRuE-AD 1 (NCT03745638)	IGA 2/3 BSA 3-20% (except for scalp)	631 (≥ 12 years)	8 weeks	Rux. 0.75%: 56.0% Rux. 1.5%: 62.1% Vehicle: 24.6%	Rux. 0.75%: 50.0% Rux. 1.5%: 53.8% Vehicle: 15.1%	Nasopharyngitis, URTI, headache
		TRuE-AD 2 (NCT03745651)	IGA 2/3 BSA 3-20% (except for scalp)	618 (≥ 12 years)	8 weeks	Rux. 0.75%: 51.5% Rux. 1.5%: 61.8% Vehicle: 14.4%	Rux. 0.75%: 39.0% Rux. 1.5%: 51.3% Vehicle: 7.6%	URTI, nasopharyngitis
Delgocitinib (Del.) Topic	pan-JAK	QBA 4-1 (JapicCTI-173554)	EASI ≥ 10 BSA 10-30%	158 (≥ 16 years)	4 weeks	Del. 0.5%: 26.4% Vehicle: 5.8%	Del. 0.5%: 10.4% Vehicle: 3.8% FACE: Del. 0.5%: 22.8% Vehicle: 4.0%	Contact dermatitis
		(JapicCTI-184064)	EASI ≥ 5 IGA 2-4 BSA 5-30%	137 (2 - 15 years)	4 weeks	Del. 0.25%: 37.7% Vehicle: 4.4%	Not reported	Nasopharyngitis, folliculitis

Upadacitinib

Upadacitinib is a selective JAK-1 inhibitor that blocks the action of the main pro-inflammatory cytokines. It has been previously approved for use in rheumatoid arthritis in several countries.

The first phase 2 study of upadacitinib for atopic dermatitis assessed the use of monotherapy at doses of 7.5 mg, 15 mg and 30 mg compared to placebo, in 167 patients aged from 18 to 75 years and diagnosed with moderate-to-severe atopic dermatitis, who were followed for 16 weeks. Patients' clinical improvement was shown to be proportionally greater as the dose increased. These findings supported the decision to maintain 15 mg and 30 mg doses in phase 3 studies. Nearly 69% of patients on upadacitinib 30 mg achieved EASI-75, followed by 52% in the group treated with 15 mg, 29% in the group using the lowest dose (7.5 mg), and 10% in the placebo group.[13,14]

Measure Up 1 and 2 were two replicate multicenter, double-blind, phase 3 trials that involved 847 and 836 volunteer patients, respectively, aged from 12 to 75 years, in more than 150 international specialized centers, who were assigned to receive upadacitinib 15 mg, upadacitinib 30 mg, or placebo, and were initially followed up for 16 weeks. In the two studies, patients who received any dose of the medication already started to have a significant improvement in EASI scores with two weeks of treatment, with 42.7% and 38.5% of patients treated with upadacitinib achieving EASI-75 in Measure Up 1 and Measure Up 2, respectively, compared with 3.6% of patients from the placebo group in both studies. At week 16, considering the sum of the populations in the two study groups, nearly 76.3% of patients treated with upadacitinib 30 mg and 64.9% of patients treated with 15 mg achieved EASI-75, compared with only 14.8% in the placebo group. Pruritus was evaluated using the NRS scale, and nearly 9.8% of patients started to have an improvement of 4 points or more as early as after 2 days of treatment with 30 mg, and 9.9% of participants after 3 days of treatment with 15 mg.[15]

The AD Up trial assessed a population of 901 patients aged 12-75 years receiving topical corticosteroids in combination with upadacitinib, allocated into three groups: upadacitinib 15 mg, upadacitinib 30 mg, or placebo. Combined medications were well tolerated by patients, and efficacy after 16 weeks was also higher in patients who used JAK inhibitor, with 77.1% of patients obtaining EASI-75 with 30 mg, and 64.6% with 15 mg, *versus* 26.4% of the placebo group. With regard to control of pruritus, 63.9% of patients receiving 30 mg achieved a 4 point reduction or more in NRS, 51.7% of patients treated with 15 mg, and only 15.0% in the placebo group at the end of 16 weeks.[16]

In the Measure Up 1 and 2 trials, the incidence of adverse effects was similar in the 15 mg and 30 mg groups. The incidence of serious infections was below 1% in all groups that received treatment. Patients who received the highest dose had more hematological changes, and up to 5% of patients in the 30 mg group presented with neutropenia in Measure Up 1, mostly transient, and none led to treatment discontinuation. In the two groups, the most frequent adverse effects were: acne (9.7% with 15 mg and 15.9% with 30 mg), upper respiratory tract infection and nasopharyngitis (14.7% with 15 mg and 18.7% with 30 mg), headache (5.7% with 15 mg and 6.9% with 30 mg), and elevation in creatine phosphokinase levels (4.5% with 15 mg and 4.9% with 30 mg). In the AD Up trial, the most common adverse effects were similar to the aforementioned ones, and there was no difference in serious adverse effects between treatment and placebo groups.[15,16]

One of the main effects observed in these two large phase 3 trials (Measure Up and AD Up) was the onset of acne vulgar (more than 5%). Most cases were of mild-to-moderate acne, with only one case of severe acne. Overall, three patients discontinued treatment due to acne. This adverse effect was more commonly observed in adult, female, and non-White patients, and its incidence was proportionally higher as the dose increased. The face was the most common location of acne. The onset of lesions occurred on nearly 40-43 days of treatment, and about 40-46% of the cases did not require additional treatment.[17] Eczema herpeticum was more reported in studies that assessed upadacitinib in atopic dermatitis than in others diseases. In the Measure Up trials, 20 patients who received medication presented with cases of herpes zoster versus only 2 patients in the placebo group.[15]

Studies were extended to observe patients using upadacitinib up to 52 weeks of treatment. In the Measure Up trial, 82.0% of patients in the 15 mg group and 84.9% of those in the 30 mg group achieved EASI-75, showing greater potential for clinical improvement with maintenance of medication for longer periods.[18] In the AD Up trial, in turn, nearly 69.0% of patients in the upadacitinib 30 mg group and 50.8% in the 15 mg group achieved EASI-75 at

week 52, with no significant changes from the results obtained at week 16, showing a slight loss of efficacy with the two doses.[19] No differences were observed in adverse effects in the two studies with more prolonged treatment. The participants of the studies continued follow-up, and further analyses are planned when completing 260 weeks of treatment.

Furthermore, upadacitinib was compared with dupilumab in a study with 692 patients aged from 18 to 75 years, divided into two groups, one receiving treatment with upadacitinib, 30 mg daily, and the other receiving dupilumab, 300 mg, every 14 days. It was observed that, at the end of 16 weeks of treatment, 60.6% patients in the group treated with JAK inhibitor achieved EASI-90, compared with 38.7% in the group who received the immunobiological agent ($p = 0.006$).[20]

Two studies were found on the PubMed platform that reported the experience of using upadacitinib in populations of specific countries. The Rising UP trial was conducted in Japan and included 272 patients aged from 12 to 75 years, receiving 15 mg, 30 mg, or placebo. Results similar to the findings of studies with international population, in which 65.3% of patients using 15 mg, and 76.2% using 30 mg, achieved EASI-75 at the end of 16 weeks.[21] In Spain, a study by Pereyra-Rodriguez et al., with a smaller sample of only 43 participants over 12 years of age, showed that 76.3% of patients treated with 30 mg and 64.9% of those treated with 15 mg achieved EASI-75. In this study, all patients below 18 years and over 65 years received 15 mg.[22]

With the promising results published, upadacitinib was approved for the treatment of atopic dermatitis in patients over 12 years by the European Union in August 2021,[23] by the FDA in January 2022,[24] and by the ANVISA in May of the same year, for use with initial doses of 15 mg/day.[25]

Abrocitinib

Abrocitinib is also a systemic selective JAK-1 inhibitor administered orally. A phase 2 study assessed 267 patients aged from 18 to 75 years for 12 weeks. They were stratified into groups receiving 200 mg, 100 mg, 30 mg, 10 mg, or placebo. The groups that received doses higher than 100 mg or 200 mg showed significant results compared with placebo, with the improvement of disease severity and pruritus, whereas patients who received lower doses did not show significant improvement.[26,27]

The group of studies named JADE is the largest phase 3 clinical trials of abrocitinib and evaluated several populations with different purposes. JADE MONO-1 was the first study to assess the effect of abrocitinib monotherapy in 387 patients aged from 12 to 75 years, predominantly with moderate atopic dermatitis. The patients were randomized to receive 100 mg, 200 mg, or placebo for 12 weeks. In this study, 62.7% of the patients treated with the highest dose, and 39.7% of those treated with the lowest dose, achieved EASI-75, versus 11.8% in the placebo group. Control of pruritus was assessed with 2 weeks of treatment, showing improvement in 46% and 20% of patients treated with 200 mg and 100 mg, respectively. This proportion increased at the end of the 12 weeks, and nearly 57.2% and 37.7% of patients showed an improvement of 4 points or more in their NRS score.[28]

With regard to adverse effects, 69% of patients treated with 100 mg, and 78% of those treated with 200 mg, reported some reaction potentially related to the treatment. The most frequent symptom was nausea, present in 20% of patients who received 200 mg, and in 9% of those who received the reduced dose, versus 3% in the placebo group. Other common symptoms were nasopharyngitis (12% with 200 mg and 15% with 100 mg), headache (10% with 200 mg and 8% with 100 mg), and upper respiratory tract infection (7% in both groups). Nearly 14% of patients treated with 100 mg presented with worsening of dermatitis symptoms. In the control group, this percentage was of 17%, and decreased to 5% in patients treated with 200 mg. Serious adverse effects that were considered related to treatment were reported for two patients, one who developed intestinal inflammatory disease while using abrocitinib 200 mg, and other who evolved with pancreatitis while using abrocitinib 100 mg, but no deaths were reported. Overall, 22 patients (14%) developed herpes virus-related infections (herpes simplex, zoster, oral, or eczema herpeticum) while receiving treatment with any dose, and only 1 patient had eczema herpeticum in the placebo group. A trend of dose-dependent thrombocytopenia was observed at nearly week 4 of treatment. One patient discontinued treatment due to persistent thrombocytopenia.[28]

JADE MONO 2 was a replicate study with 391 patients that used the same methodology as the previous one and showed similar results. At the end of 12 weeks, 61% of patients treated with 200 mg and

44.5% of those treated with 100 mg achieved EASI-75. Control of pruritus was also similar, and median time for improvement was 29 days in the 200 mg group and 58 days in the 100 mg group.[29]

With regard to IGA score, in the JADE MONO 1 trial, 43.8% of patients treated with 200 mg and 23.9% of those treated with 100 mg achieved IGA 0/1 in the analysis of the 12 weeks of treatment. In JADE MONO 2, even few patients achieved the target, with 38.1% in the 200 mg group and 28.4% in the 100 mg group. Overall, nonresponders according to the IGA score had more severe atopic dermatitis at baseline. Considering the entire population assessed in the phase 2b study, along with that assessed in JADE MONO 1 and 2 trials, a higher percentage of patients who achieved the desired IGA score was classified as having moderate atopic dermatitis at baseline, compared with nonresponders (72.7% versus 58.8% of patients with IGA 3 at baseline). When considering other scales to asses dermatitis, many patients who did not achieve the target IGA score obtained improvement in clinical status and in scores of others tools, suggesting that the assessment of drug efficacy by IGA may be limited. Among nonresponders according to the IGA score, 41.0% of those who received abrocitinib 200 mg were found to achieve EASI-75 at week 12, followed by 27.0% of those who received abrocitinib 100 mg.[30]

The JADE REGIMEN trial was designed to assess maintenance therapy. Firstly, patients with moderate/severe atopic dermatitis were selected to receive treatment with abrocitinib 200 mg for 12 weeks. At end of period, only responder patients were stratified, considering IGA, EASI and NRS scores, into three groups: the first would continue to receive 200 mg, other would receive 100 mg, and the last would receive placebo, to be evaluated for 40 weeks. During this period, the rate of failure of maintenance treatment was significantly higher in the 100 mg group compared with the group that received the highest dose (HR 0.36; $p < 0.0001$). It was observed that 39.6% of patients treated with 100 mg and 16.5% of those treated with 200 mg had a therapeutic flare, defined as a 50% reduction in EASI compared to that obtained at week 12 or IGA score of 2 or more. With regard to placebo, the two groups who received the medication exhibited a significant decrease in the rate of therapeutic flare, whereas 77.5% of the patients in the placebo group had a flare.[31]

The JADE COMPARE trial assessed 837 patients randomized to receive abrocitinib 100 mg or 200 mg, dupilumab 300 mg, or placebo. There was no difference in the outcome of patients treated with abrocitinib 100 mg and dupilumab – in both groups, 36% of patients had an IGA score of 0/1 and 58% achieved EASI-75 after 12 weeks of treatment. However, patients in the abrocitinib 200 mg group showed better results, with 48% of them having an IGA 0/1 and 70% achieving EASI-75. The patients with the highest dose present with slightly more mild adverse effects, such as nausea.[32] With regard to time to clinical improvement, patients using abrocitinib 200 mg also had better results, with a mean of 29 days to achieve EASI-75. In the group of 100 mg, mean time to achieve EASI-75 was 32 days, and could reach up to 57 days for improvement of lesions in head, neck, and upper limbs, a result similar to that of the dupilumab group.[33]

Patients treated with dupilumab after 12 weeks were randomized again to receive treatment with abrocitinib 100 mg or 200 mg until completing 40 weeks of treatment. Of the 54 patients who obtained an improvement of 75 to 90% in EASI with dupilumab, 61.1% achieved EASI-90. Of the 29 patients who did not respond to dupilumab, 8 showed improvement by changing medication. However, some patients who had responded to dupilumab, achieving EASI-75, IGA 0/1 and/or improvement of 4 points or more in the NRS score, did not maintain response using abrocitinib, at percentages ranging from 7.6% to 23.1%, depending on the dose and on the scale used.[34]

JADE MONO 1 and 2 trials included a small portion of adolescents from 12 to 17 years (21.7% and 10.2% of the sample, respectively). The findings in these populations followed the trend of efficacy observed in the general population, with 54.5% and 60% of patients in JADE MONO 1 and 2 achieving EASI-75 with abrocitinib 200 mg, and 44.1% and 43.8% with abrocitinib 100 mg, respectively. The JADE TEEN trial included 295 adolescents and showed that the difference in results between the different doses was smaller (EASI-75 in 72.0% with 200 mg, and in 68.5% with 100 mg). However, the participants in this study could combine abrocitinib with a topical drug, which was also related to the fact that a higher percentage of patients in the control group showed better clinical response, since 24.5% of patients who received placebo achieved EASI-75 within weeks.[35,36]

The drug was also approved for use in patients with atopic dermatitis by the FDA for patients over 18 years in the United States in January 2022.[37]

Baricitinib

Baricitinib is a JAK-1 and 2 inhibitor, and its use in atopic dermatitis has been studied since 2016, when phase 2 studies started.[38] The BREEZE-AD program includes 7 phase 3 studies to assess baricitinib efficacy. The first studies, named BREEZE-AD 1 and 2, were two double-blind identical studies that analyzed 624 and 615 participants, respectively, over 18 years of age for 16 weeks, who received placebo or baricitinib 1 mg, 2 mg, or 4 mg. In these first studies, the use of the JAK inhibitor pruritus severity with doses of 2 mg and 4 mg, but improvements in EASI were not equally relevant.[39]

BREEZE 4 included 463 participants over 18 years of age to analyze patients' response to baricitinib combined with topical corticosteroids versus placebo. Patients who received 4 mg of the medication achieved EASI-75 in 32% of the cases, whereas 28% of those who received 2 mg reached EASI-75, with no significant difference from placebo (17%).[40]

BREEZE 5 is a study that includes only the American and Canadian population, with 440 participants, and analyses the effect of smaller doses of baricitinib 1 mg and 2 mg compared with placebo. It was observed that only baricitinib 2 mg had a significant result compared with placebo, after 16 weeks of use, EASI-75 and IGA score of 0/1 in was achieved by 37.1% and 31.7% of baricitinib 2-mg-treated patients with body surface area affected from 10-50, compared with 9.9% and 6.9%, respectively, in the placebo group ($p < 0.001$). In patients with greater body surface area affected and receiving 1 mg, there were no significant differences with regard to placebo.[41,42]

Among the 329 patients of BREEZE 7, nearly 31% of those who received 4 mg had an IGA score of 0/1, compared with 15% of those in the placebo group. The difference between the baricitinib 2 mg and placebo groups were not statistically significant also, considering the IGA score. Furthermore, it was observed that 48% and 43% of 4-mg and 2-mg-treated patients, respectively, achieved EASI-75, versus 23% of those in the placebo group.[43]

Considering all the studies, the percentage of patients who achieved EASI-75 with baricitinib 4 mg in the BREEZE AD 1, 2, 4 and 7 trials was 24.8%, 21.1%, 31.1%, and 47.7%, respectively. These results are inferior when compared with other JAK inhibitors.[44] In an indirect comparison with previous studies using dupilumab, the BREEZE trials were not able to show superior results as compared with the immunobiological agent (51% of the sample achieved EASI-75 in SOLO 1, and 44% in SOLO 2, studies that validated dupilumab in atopic dermatitis).[45-46]

Although having a lower reported efficacy compared with the other two oral JAK inhibitors in phase 3 studies for atopic dermatitis, baricitinib was the first JAK inhibitor approved for eczema in Europe, in September 2020.[44]

Ruxolitinib

Ruxolitinib is a JAK-1 and JAK-2 topical inhibitor developed to optimize drug action directly on the affected areas and reduce the risk of systemic adverse effects. In a phase 2 study, ruxolitinib promoted a rapid and sustained improvement of lesions, and no significant adverse effect was observed.[47] This study was conducted in the United States and Canada and evaluated 307 patients aged from 18 to 70 years to compare the effect of topical ruxolitinib at doses of 0.15%, 0.5%, and 1.5%, once or twice daily, with 0.1% triamcinolone and vehicle. Patients were initially assessed for a period of 4 weeks, and medications were not applied on the facial region. After the first month of treatment, lower concentrations of ruxolitinib did not lead to superior results compared with topical corticosteroids. Among patients who received ruxolitinib 1.5% twice daily, 56% achieved EASI-75, versus 47.1% in the corticosteroid group and 17.3% in the vehicle group. After week 4, patients who received triamcinolone used vehicle for 4 weeks and, after week 8, all patients received ruxolitinib 1.5% twice daily until completing 12 weeks of analysis. At that time, 73.2% of the 252 patients who completed the study achieved EASI-75, which indicates that changing to the topical JAK inhibitor led to additional improvement of lesions.[48]

The TRuE-AD 1 and 2 trials were two parallel, double-blind, phase 3 studies that assessed the effect of topical ruxolitinib in patients over 12 years of age with mild/moderate atopic dermatitis, evaluated for 8 weeks. Overall, 631 patients were randomized in TRuE-AD 1, and 616 patients in TRuE-AD 2, to receive ruxolitinib cream 0.75%, 1.5% or a vehicle cream with no active compound, applied twice daily.[49]

The two concentrations of ruxolitinib led to an improvement in lesions compared with vehicle. Among patients who used ruxolitinib 0.75% in TRuE-AD 1, 50% had an IGA score of 0/1 and 56% achieved EASI-75; conversely, among individuals who received

ruxolitinib 1.5%, 53.8% had an IGA score of 0/1, and 62.1% achieved EASI-75. In the TRuE-AD 2, it was found that 39% and 51.5% of patients who received the lowest concentration of the drug achieved an IGA score of 0/1 and EASI-75, respectively; whereas 51.3% of those who received the highest dose achieved an IGA score of 0/1, and 61.8% of them achieved EASI-75. In the vehicle group, 15.1% and 24.6% of patients reached an IGA score of 0/1 and EASI-75 in TRuE-AD 1, and 7.6% and 14.4% achieved the targets for IGA score and EASI in TRuE-AD 2, respectively.[49]

The most common adverse effect observed in the study was application site burning sensation, which was reported in a higher percentage of patients in the vehicle group (4.4% versus 0.6% with ruxolitinib 0.75% and 0.8% with ruxolitinib 1.5%). No serious adverse effect was related to the use of the medication.[49]

In September 2021, ruxolitinib was approved for use in atopic dermatitis by the FDA, being the first JAK inhibitor approved for use in the United States, at a concentration of 1.5%, in patients over 12 years of age.[50]

Delgocitinib

Delgocitinib is a topical pan-Janus Kinase inhibitor, i.e., it inhibits JAK-1, JAK-2, JAK-3, and TYK-2. Results of phase 1, 2 and 3 studies conducted in Japan were found. In phase 1 studies, the drug was tested in adults, and topical application showed to be safe, with no immediate local reactions and apparent improvement after 7 days of use.[50]

A phase 2 study involved 38 centers and included 366 participants aged from 16 to 65 years randomized to receive delgocitinib at 0.25%, 0.5%, 1%, or 3%, or the vehicle ointment, or tacrolimus 0.1% for 4 weeks. The vehicle group showed the highest rates of patients requiring rescue therapy, and these rates progressively decreased as the dose of delgocitinib increased. In this study, 23% of patients treated with delgocitinib 3% achieved an IGA score of 0/1, compared with 3% of those in the vehicle group. Only the highest dose of delgocitinib showed equal or superior results as compared to tacrolimus.[51]

Furthermore, a phase 2 study assessed the use of delgocitinib in the pediatric population, including 103 patients aged from 2 to 15 years with EASI greater than 5, excluding the head/neck region, IGA score equal or higher than 2, and eczema affecting 5 to 30% of the body surface area. Patients were randomized to receive delgocitinib 0.25%, 0.5%, or vehicle. At the end of 4 weeks, EASI-75% was achieved by 50% of patients in the delgocitinib 0.5% group, 38.2% of those in the 0.25% group, and 8.6% of those in the control group. Improvement of pruritus were already observed at week 1 of treatment, with the two doses.[52]

The phase 3 study with the pediatric population had two parts. In part 1, 137 patients were randomized to receive delgocitinib 0.25% or vehicle for 4 weeks, and 37.7% of patients receiving medication achieved EASI-75, compared to 4.4% of those in the control group. In part 2, patients were followed up for more 52 weeks while receiving delgocitinib 0.25% or 0.5%. Nearly 52.5% of patients achieved EASI-75. Treatment-related adverse effects were reported in 9.7% of patients, all of which were mild. The most common one was application site folliculitis, and one patient discontinued treatment due to acne.[53]

Patients over 16 years of age were also included in phase 3 studies. The QBA4-2 study assessed the patients for 52 weeks, when all patients received delgocitinib 0.5%, without any control group. The proportion of patients who achieved EASI-75 was 10.9%, at week 4 and 27.5% at week 52. Serious adverse effects occurred in 1.4% of patients. One participant presented with Kaposi's varicelliform eruption that was considered related to the application, which developed on day 26 of treatment, and had to interrupt medication. Nearly 3.4% of patients discontinued treatment due to adverse effects, the most common of which was contact dermatitis.[54,55]

Delgocitinib was approved for topical use in atopic dermatitis in Japan, at the concentrations of 0.25% and 0.5%, for the adult population and children over two years of age, in March 2021.[55]

Conclusion

The use of JAK inhibitors has recently started to be regulated for use in atopic dermatitis in clinical practice across different countries. This type of small molecules showed promising results in the treatment of several diseases, such as cancer and autoimmune, viral, and allergic diseases. However, like all new medications, attention should be given to their potential adverse events. By studying the mechanism of action of these drugs, it is possible to raise concerns with regard to the remaining potential effects in other systems that these drugs may eventually affect. The JAK-STAT pathway is known to be present not only in type 2 inflammation, but also participates in the

modulation of other extremely important functions, such as immunity and hematopoietic pathways. When properly indicated, the use of JAK inhibitors yielded positive results, some of which were superior to those of recommended treatments for the control of atopic dermatitis.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Quality of life according to asthma control and severity in pediatric patients at a hospital in Belém do Pará, north of Brazil

Qualidade de vida de acordo com o controle e gravidade da asma em pacientes pediátricos atendidos em um hospital em Belém do Pará

Maria Emilia da Silva Coelho[1], Gabriele Arja de Abreu[1], Mariane Cordeiro Alves Franco[1], José Tadeu Colares Monteiro[2], Lilian França dos Santos Monteiro Pereira[3]

ABSTRACT

Background: Asthma is a chronic obstructive inflammatory disease that, even with low mortality, can impair the quality of life (QoL) of children and adolescents. Establishing to what extent asthma severity and control can influence patient QoL may contribute to better patient outcomes. **Objective:** To evaluate the QoL of children with asthma according to disease severity and symptom control. **Methods:** This was a cross-sectional study of asthmatic children aged 7 to 13 years followed up at the pediatric pulmonology outpatient clinic of Hospital Fundação Santa Casa de Misericórida do Pará (FSCMPa). Sociodemographic and clinical data were obtained using an identification form and from medical records. Symptom control was assessed by the Asthma Control Test, and severity was determined using the Global Initiative for Asthma criteria. The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) was used to assess QoL. **Results:** We interviewed 45 patients (57.7% boys) with a mean age of 9.53 ± 1.89 years (median, 9 years). Of these, 19, 11, and 15 were classified as having well-controlled, partially controlled, and uncontrolled asthma, respectively. As for severity, 25, 19, and 1 were classified as having mild, moderate, and severe asthma, respectively. Children with well-controlled asthma had higher scores in total and in all domains of the PAQLQ than those with partially controlled or uncontrolled asthma ($p<0.05$). Regarding treatment adherence, patients with good adherence were approximately 3 times more likely to have minimal or no impairment in QoL than those with poor adherence. **Conclusion:** Asthmatic children have impaired QoL as a result of inadequate symptom control and non-adherence to treatment.

Keywords: Asthma, quality of life, child.

RESUMO

Introdução: A asma é uma doença inflamatória obstrutiva crônica que, mesmo com baixa letalidade, pode prejudicar a qualidade de vida das crianças e adolescentes. Estabelecer o quanto a gravidade da asma e o seu controle podem influenciar na qualidade de vida dos pacientes pode auxiliar em um melhor desfecho para os pacientes. **Objetivo:** Avaliar a qualidade de vida em crianças asmáticas de acordo com o controle de sintomas e a gravidade da doença. **Métodos:** Estudo transversal com inclusão de crianças asmáticas de 7 a 13 anos de idade acompanhadas no ambulatório de pneumologia pediátrica da Fundação Santa Casa de Misericórdia do Pará (FSCMPa). Dados sociodemográficos e clínicos foram obtidos por meio de uma ficha de identificação e do prontuário. O controle de sintomas foi avaliado pelo Teste de Controle da Asma e a gravidade foi determinada com base nos critérios do Global Initiative for Asthma. Para avaliação da qualidade de vida foi utilizado o *Paediatric Asthma Quality of Life Questionnaire* (PAQLQ). **Resultados:** Foram entrevistados 45 pacientes (57,7% meninos) com média de idade de 9,53±1,89 e mediana de 9 anos. Destes, 19, 11 e 15 foram classificados, respectivamente, com asma controlada (AC), asma parcialmente controlada (APC) e asma não controlada (ANC). Quanto à gravidade, 25, 19 e 1 foram classificados, respectivamente, com asma leve (AL), asma moderada (AM) e asma grave (AG). O grupo AC, quando comparado ao APC e ANC, apresentou maiores valores no escore geral do PAQLQ e em todos os domínios ($p < 0,05$). Quanto à adesão ao tratamento, verificou-se que pacientes com adesão terapêutica têm aproximadamente três vezes mais chance de ter prejuízo mínimo ou ausente na qualidade de vida do que pacientes não aderentes. **Conclusão:** Crianças asmáticas têm comprometimento da qualidade de vida relacionado ao inadequado controle dos sintomas e à não adesão terapêutica.

Descritores: Asma, qualidade de vida, criança.

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Introduction

According to the Global Initiative for Asthma (GINA) guidelines, asthma is a chronic obstructive inflammatory disease characterized by lower airway hyperresponsiveness and variable airflow limitation.[1] Clinical manifestations include recurrent episodes of coughing, wheezing, dyspnea, and chest pain, predominantly during the day and at night. Symptoms may be reversed spontaneously or with the use of medications.[2]

Asthma affects approximately 1% to 18% of the population in different countries.[1] Despite therapeutic advances and a better understanding of the pathogenesis of asthma, the global prevalence has been increasing in the last two decades, and one-third of those affected are aged < 18 years.[3]

There are approximately 20 million people with asthma in Brazil, which is one of the countries with the highest prevalence of the disease in children, with high rates of severe asthma.[4] Because asthma is the most frequently treated chronic disease in emergency services in the pediatric age group, it has major economic impacts.[5] According to the Brazilian Unified Health System (Sistema Único de Saúde, SUS) Database (DATASUS), asthma hospitalizations in the age group from 0 to 19 years cost a total of 31,844,124.84 for the public health care system.[6]

Uncontrolled asthma is expensive for the health care system as well as for families. Costs related to severe asthma are estimated to correspond to more than a quarter of family income among SUS users, and disease control would substantially reduce this burden.[7]

Adequate management of drug therapy combined with asthma education for patients and their caregivers are critical for disease control.[8] In addition, follow-up with periodic patient evaluation, aiming at asthma control, is important to determine the level of the disease and whether the treatment plan needs to be adjusted.[7]

Quality of life (QoL) is associated with symptom control and asthma severity. Despite low mortality, asthma can impair the QoL of affected children and adolescents, as well as of their caregivers, due to reasons such as unstable health conditions, need for prolonged treatments, side effects of medications, and constant visits to doctors and emergency services.[9]

The assessment of health-related QoL (HRQoL) using pediatric questionnaires has been encouraged in clinical follow-up to provide a holistic understanding of health in this age group.[10] Knowledge of the extent to which asthma severity and control may affect QoL can help establish therapeutic, behavioral, and environmental strategies in the health care system that could improve the outcomes of patients with asthma.[11]

Although QoL assessment is recommended for an adequate clinical follow-up, studies focused on pediatric patients with asthma are still lacking. The present study aimed to evaluate QoL according to symptom control and asthma severity in pediatric patients with asthma treated at a hospital in Belém do Pará, Brazil.

Methods

This analytical, cross-sectional clinical study was conducted in an outpatient pediatric pulmonology service in Belém do Pará from April to December 2019. All children and adolescents aged 7 to 14 years with a previous diagnosis of asthma who attended outpatient care during the study period were included. Absent patients, patients with comorbidities affecting their general condition, patients undergoing outpatient follow-up due to other pulmonary diseases, and those with cognitive impairment that precluded the application and understanding of tests were excluded.

Parents and legal guardians, as well as children and adolescents, were invited to participate in the study before the medical visit and were properly informed of all study procedures. All participants and their respective legal guardians who agreed to participate signed assent and informed consent forms, respectively.

An identification and basic assessment form was initially applied to parents with the aim of obtaining the following information: participant age, sex, origin (urban or rural area), weight and height (information obtained from the outpatient visit that occurred on the same day), personal morbid history, family history (asthma, rhinitis, sinusitis, current smoking by a caregiver), number of asthma attacks in the last year and in the last 3 months, treatment adherence, and discontinuation of medication in the absence of symptoms or in the presence of any undesirable effects related to medication use.

The Asthma Control Questionnaire (ACT) was subsequently applied, consisting of 5 questions regarding signs and symptoms of asthma, use of

rescue medication in the last 4 weeks, and perception of asthma control. The scores of the 5 questions were summed to obtain the total score, according to definitions by the 2020 Recommendations for Asthma Management of the Brazilian Society of Pulmonology and Phthisiology:

– Scores ≥ 20: controlled asthma.
– Scores 16-19: partially controlled asthma.
– Scores ≤ 15: uncontrolled asthma.

Asthma severity was assessed retrospectively by analyzing the medical records of included patients according to the adopted treatment regimen. Those with mild asthma required mild treatment for asthma control (stage 1 and stage 2), those with moderate asthma required moderate treatment (stage 3), and those with severe asthma required intense treatment (stage 4 and stage 5).

QoL was assessed using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ), which is destined for patients with asthma aged between 7 and 17 years. The questionnaire is composed of 23 questions grouped into 3 domains:

– Activity limitation: five questions about the discomfort caused by asthma when performing certain activities.
– Symptoms: 10 questions about the discomfort caused by seizures, coughing, dyspnea, wheezing, chest tightness, and nocturnal awakening.
– Emotional function: eight questions about the frequency with which the disease makes the patient feel angry, feel different from others, feel fear due to an eventual asthmatic attack, and feel irritated or upset for not being able to keep up with other people's rhythm.

All items have equal weight. The score and arithmetic mean corresponding to each domain were calculated to obtain the individualized score, as well as the arithmetic mean of the 23 questions to obtain the general QoL score. To establish to what extent asthma severity and control can influence QoL in children and adolescents, the following definitions were considered:

– Scores ≥ 6: minimal or no impairment.
– Scores < 6 and ≥ 3: moderate impairment.
– Scores < 3: severe impairment.

The sample was analyzed using descriptive statistics by measures of central tendency (arithmetic mean and median), variance (standard deviation), and absolute and relative frequencies. Continuous variables were analyzed using the Kruskal-Wallis test (with Dunn's post-test in case of statistical significance) or Mann-Whitney test, according to the number of analyzed groups. Categorical variables were analyzed using the G test. For dichotomous categorical variables, the odds ratio was assessed, considering a 95% CI. All statistical inference was performed on BioEstat 5.4. A p-value ≤ 0.05 was considered significant.

The study was approved by the Research Ethics Committee under decision no. 3.238.653.

Results

From April to December 2019, 190 patients received care at the pediatric outpatient service in question. Of these, 45 were eligible for the survey and were interviewed. Among the 145 patients who were not eligible, 76 were outside the age group and 69 were in one of the following categories: follow-up for another pulmonary disease, presence of comorbidities with systemic repercussions, or cognitive impairment that precluded the understanding of research procedures.

The sample consisted of 26 boys (57.7%) and 19 girls (42.2%). Mean patient age was 9.53 ± 1.89, with a median of 9 (7-13.9) years. Mean body mass index (BMI) was 18.5 ± 3.61, with a median of 17.92. Mean height was 139.46 ± 12.59, with a median of 141.

Regarding patients' personal morbid history, 41 (91%) had allergic rhinitis in addition to asthma and 17 (37.7%) had a history of hospitalization due to asthma. As for family history, 35 patients (77.7%) had a positive history for asthma and 31 (68.8%) for allergic rhinitis.

ACQ results showed that 19 patients (42.2%) had controlled asthma, 11 had partially controlled asthma (24.4%), and 15 (33.3%) had uncontrolled asthma. Regarding asthma severity, 25 (55.5%) had mild asthma, 19 (42.2%) had moderate asthma, and only 1 patient (2.2%) had severe asthma.

Of patients with controlled asthma, 14 (73.6%) had mild asthma, 4 (21%) had moderate asthma, and 1 (5.2%) had severe asthma. In the partially controlled asthma group, 7 patients (63.63%) had moderate asthma and 4 (36.3%) had mild asthma. In the uncontrolled asthma group, 8 patients (53.3%) had moderate asthma and 7 had mild asthma (46.6%). The controlled asthma group was significantly associated

with the mild asthma group ($p < 0.05$), meaning that those with controlled asthma were more likely to be classified as having mild asthma. Other levels of symptom control and asthma severity were not significantly associated in the present study. Age, BMI, and height were not associated with symptom control and asthma severity, meaning the groups are comparable.

Regarding the association between symptom control and QoL assessed by the PAQLQ, the controlled asthma group had significantly improved scores in the overall score and in all domains than the partially controlled and uncontrolled asthma groups ($p < 0.05$). Score distribution of the PAQLQ domains with the mean score, standard deviation, and median of each domain is shown in Table 1.

In the present study, the PAQLQ score was not significantly associated with asthma severity, and the mild, moderate, and severe asthma groups were comparable in this regard, as shown in Table 2.

QoL impairment according to asthma control and severity is reported in Tables 3 and 4, respectively. In the overall score, 25 (55.5%) of patients had minimal or no impairment, 18 (40%) had moderate impairment, and 2 (4.4%) had severe impairment. Symptom control was significantly associated ($p < 0.05\%$) with QoL impairment in the general score in the domains of activity limitation and emotional function. The same association was not observed in the domain of asthma symptoms and control, and asthma severity was not associated with QoL impairment in the present study ($p > 0.05\%$).

Among patients with minimal or no impairment on the PAQLQ, 16 (64%) were in the controlled asthma group, whereas 85% of patients with moderate to severe impairment were in the partially controlled and uncontrolled asthma groups. Regarding asthma severity, 68% of patients with mild asthma had minimal or no impairment in QoL, whereas 63.16% of patients with moderate asthma had moderate to severe impairment.

In the domain of activity limitation, 24 (53.3%) of participants had minimal or no impairment, 17 (37.7%) had moderate impairment, and 4 (8.8%) had severe

Table 1
Score distribution of the Paediatric Asthma Quality of Life Questionnaire domains according to level of asthma control

Variable	Group	Mean	SD	Minimum	Median	Maximum	p-value*
Overall	CA	6.51	0.81	3.69	6.91	7.00	0.0083
	UA	5.13	1.65	2.95	5.21	7.00	
	PCA	4.98	1.50	2.82	4.86	7.00	
Activity limitation	CA	6.34	1.10	3.40	7.00	7.00	0.0160
	UA	4.84	1.91	2.20	4.60	7.00	
	PCA	5.16	1.31	2.80	5.00	7.00	
Symptoms	CA	6.61	0.67	5.00	7.00	7.00	0.0035
	UA	5.21	1.53	2.40	5.40	7.00	
	PCA	5.18	1.60	2.70	5.80	7.00	
Emotional function	CA	6.62	0.74	3.87	7.00	7.00	0.0497
	UA	5.39	1.70	2.50	6.00	7.00	
	PCA	5.12	1.69	2.62	4.75	7.00	

CA = controlled asthma (n = 19), UA = uncontrolled asthma (n = 15), PCA = partially controlled asthma (n = 11).
* Kruskal-Wallis test.

impairment. Of those with minimal impairment, 15 (62.5%) were in the controlled asthma group and 16 (66.6%) were in the mild asthma group. Of those with moderate to severe impairment, 17 (80.95%) were in the partially controlled and uncontrolled asthma groups and 12 (57.14%) were in the moderate asthma group.

In the domain of symptoms, 26 (57.7%) participants had minimal or no impairment, 17 (37.7%) had moderate impairment, and 2 (4.4%) had severe impairment. Sixteen patients (61.53%) with minimal or no impairment had controlled asthma and mild asthma, respectively. Of the 19 patients with moderate to severe impairment, 16 (84.2%) had partially controlled and uncontrolled asthma and 10 (52.63%) had moderate asthma.

Regarding the domain of emotional function, 30 (66.6%) participants had minimal or no impairment, 13 (28.8%) had moderate impairment, and 2 (4.4%) had severe impairment. Eighteen (60%) patients with minimal or no impairment were in the controlled asthma group and had mild asthma. Fourteen (93.3%) patients in the moderate to severe impairment group had partially or uncontrolled asthma and 8 (53, 3%) had moderate asthma.

Treatment adherence was associated with impaired QoL. As shown in Table 5, taking into consideration the overall PAQLQ score, a patient with adequate treatment adherence would be approximately 2.66 times more likely to have minimal or no impairment than a patient with treatment nonadherence. The same association was observed between treatment adherence and the other domains.

Discussion

Obtaining a complete evaluation of the health status of a child includes, in addition to clinical parameters, the assessment of HRQoL,[12] given that better disease control is associated with improved QoL in children.[13] However, the lack of targeted or adapted instruments to other cultures constitutes a major obstacle.[12]

Table 2
Score distribution of the Paediatric Asthma Quality of Life Questionnaire domains according to level of asthma severity

Variable	Group	Mean	SD	Minimum	Median	Maximum	p-value*
Overall	MA	5.92	1.42	2.95	6.69	7.00	0.1966
	ModA	5.28	1.51	2.82	5.43	7.00	
	SA	–	–	–	–	–	
Activity limitation	MA	5.79	1.59	2.60	6.60	7.00	0.1807
	ModA	5.16	1.57	2.20	5.00	7.00	
	SA	–	–	–	–	–	
Symptoms	MA	6.02	1.36	2.40	6.80	7.00	0.1731
	ModA	5.44	1.47	2.70	5.90	7.00	
	SA	–	–	–	–	–	
Emotional function	MA	6.04	1.35	3.00	6.75	7.00	0.3313
	ModA	5.53	1.68	2.50	6.25	7.00	
	SA	–	–	–	–	–	

MA = mild asthma (n = 25), ModA = moderate asthma (n = 19), SA = severe asthma (n = 1).
* Mann-Whitney test.

The PAQLQ was developed with the objective of measuring QoL in children and adolescents. When correctly applied, it can detect subtle changes in QoL,[14] and is currently the only instrument with complete cultural validation and adaptation for measuring QoL in pediatric patients with asthma in Brazil.[12] A 20-year study with patients with asthma and their caregivers showed that children and adolescents with asthma have worse QoL compared with those without asthma.[15]

Patient age has been associated with symptom control, asthma severity, and QoL in pediatric patients from Egypt[16] and Serbia,[17] where increased asthma severity was associated with increased QoL impairment in older children. Such association was not observed in this study nor in previous studies conducted in Brazil,[11] Lebanon,[18] and Nigeria.[19]

BMI was not significantly associated with symptom control, asthma severity, or QoL, which is in accordance with the results obtained by Matsunaga[11] and El-Gilany.[20] A Danish study,[21] however, found an association between BMI, symptom control, and asthma severity, which were proportional to the BMI of the study participant.

The association between symptom control and QoL in children and adolescents with asthma is well documented, with poorer symptom control being associated with a decrease in QoL rates.[5,16,18,22] This association was observed in our study population, in which worse ACT scores were associated with lower overall score as well as lower scores in all PAQLQ domains. In the present study, the overall PAQLQ score and all PAQLQ domain scores were associated with symptom control, as demonstrated in

Table 3
Distribution of asthma cases according to level of asthma control and reported type of impairment in the Paediatric Asthma Quality of Life Questionnaire domains

Variables	CA n (%)	UA n (%)	PCA n (%)	p-value*
Overall				
Minimum or none	16 (84.21)	6 (40.00)	3 (27.27)	
Moderate	3 (15.79)	8 (53.33)	7 (63.64)	0.0301
Severe	–	1 (6.67)	1 (9.09)	
Activity limitation				
Minimum or none	15 (78.95)	6 (40.00)	3 (27.27)	
Moderate	4 (21.05)	6 (40.00)	7 (63.64)	0.0243
Severe	–	3 (20.00)	1 (9.09)	
Symptoms				
Minimum or none	16 (84.21)	6 (40.00)	4 (36.36)	
Moderate	3 (15.79)	8 (53.33)	6 (54.55)	0.0601
Severe	-	1 (6.67)	1 (9.09)	
Emotional function				
Minimum or none	18 (94.75)	8 (53.33)	4 (36.36)	
Moderate	1 (5.26)	6 (40.00)	6 (54.55)	0.0167
Severe	–	1 (6.67)	1 (9.09)	

CA = controlled asthma (n = 19), UA = uncontrolled asthma (n = 15), PCA = partially controlled asthma (n = 11).
* G test.

Table 4
Distribution of asthma cases according to level of asthma severity and reported type of impairment in the Paediatric Asthma Quality of Life

Variables	MA n (%)	ModA n (%)	SA n (%)	p-value*
Overall				
Minimum or none	17 (68.00)	7 (36.84)	1	
Moderate	7 (28.00)	11 (57.90)	–	0.6290
Severe	1 (4.00)	1 (5.26)	–	
Activity limitation				
Minimum or none	16 (64.00)	7 (36.84)	1	
Moderate	7 (28.00)	10 (52.63)	–	0.5959
Severe	2 (8.00)	2 (10.53)	–	
Symptoms				
Minimum or none	16 (64.00)	9 (47.37)	1	
Moderate	8 (32.00)	9 (47.37)	–	0.8966
Severe	1 (4.00)	1 (5.26)	–	
Emotional function				
Minimum or none	18 (72.00)	11 (57.89)	1	
Moderate	7 (28.00)	6 (31.58)	–	0.7191
Severe	–	2 (10.53)	–	

MA = mild asthma (n = 25), ModA = moderate asthma (n = 19), SA = severe asthma (n = 1).
* G test.

other studies.[5,11,20,23] However, two domains are often more affected than the others depending on the study population: activity limitation and symptoms.[24]

Unlike other studies in which the symptoms domain was the most affected,[5,16,19] the activity limitation domain was the most affected in the present study, as well as in a study conducted in Portugal.[25] This may be explained by different perceptions of activity limitation, level of physical activity, different inclusion criteria, and adequate clinical follow-up.[5,16]

In the present study, asthma severity was not significantly associated with QoL, which is consistent with studies from Israel[26] and Turkey.[13] Because the classification of asthma severity is related to the intensity of the therapeutic regimen, severity categorization may differ according to different health care services and adherence to different therapeutic measures.[26] In addition, the lack of correlation between severity and QoL observed in this and other studies may be associated with the small number of participants with severe asthma (only 1 in this study) or the relatively limited study sample. However, other studies have reported an association between QoL and level of asthma severity,[5,11,19,24] although some of these studies used other tools to assess asthma severity, which could explain the different results.

Allergic rhinitis is a highly prevalent comorbidity among patients with asthma,[3,5,27] as demonstrated in this study, in which 91% of participants reported having both conditions. Such association was also reported in previous studies from Brazil and Latin America,[3,27] in which most participants reported having both conditions. Because rhinitis may also affect QoL in children with asthma, the concept of a

single airway should be adopted more frequently for adequate disease management.[5]

In chronic diseases such as asthma, adequate adherence to treatment is crucial for achieving the clinically expected results. In this study, adherence to maintenance and rescue therapies was subjectively measured[28] by asking caregivers about current medications and comparing the data with prescription information obtained from medical records. The adherence rate was 71.1%, differing from a large-scale Brazilian study on adherence to asthma treatment[29] that reported a mean rate of 52%. However, our results were comparable to the variable rate found by a Belgian study, in which adherence levels ranged up to 70%.[28]

In the present study, adequate medication adherence was associated with QoL, and patients with inadequate adherence were more likely to have impaired QoL. Such association was also reported by the ADERE study,[29] which found a positive association between treatment adherence and QoL in those with asthma. However, a study conducted in a specialized outpatient clinic in the state of São Paulo did not find this association.[5]

Some caregivers reported the high cost of maintenance therapy as a contributing factor to lower adherence, especially long-acting beta-2-agonists. In previous studies, financial restrictions and the high cost of medications were also reported as important factors that contributed to lower medication adherence.[28,29]

For persistent and lasting improvement in symptom control and QoL in patients with asthma, continuous follow-up is required,[13,16] given that patients with periodic follow-up have improved rates of asthma control over time.[3] Thus, monitoring QoL rates in patients with asthma is important because worse rates are directly associated with decreased

Table 5
Adherence to asthma treatment according to QoL impairment assessed by the Paediatric Asthma Quality of Life Questionnaire

Associated factors	QoL impairment		Odds ratio	95% confidence interval	p-value
	None/minimum (%)	Moderate/severe (%)			
Overall					
Treatment adherence	20 (80.00)	12 (60.00)	2.6667	0.71-10.05	0.2543
Treatment nonadherence	5 (20.00)	8 (40.00)			
Total	25 (100.00)	20 (100.00)			
Activity limitation					
Treatment adherence	19 (79.17)	13 (61.90)	2.3385	0.72-8.77	0.3447
Treatment nonadherence	5 (20.83)	8 (38.10)			
Total	24 (100.00)	21 (100.00)			
Symptoms					
Treatment adherence	21 (80.77)	11 (57.89)	3.0545	0.80-11.60	0.1805
Treatment nonadherence	5 (19.23)	8 (42.11)			
Total	26 (100.00)	19 (100.00)			
Emotional function					
Treatment adherence	23 (76.67)	9 (60.00)	2.1905	0.58-8.33	0.4157
Treatment nonadherence	7 (23.33)	6 (40.00)			
Total	30 (100.00)	15 (100.00)			

symptom control.[23,30] This strategy may facilitate clinical decisions and guide the establishment of more effective treatment regimens.[30]

Study limitations include the limited number of participants and the cross-sectional nature of the study, which lacked long-term patient follow-up. In addition, we only included 1 patient with severe asthma. Another possible limitation is the subjective assessment of treatment adherence, meaning that adherence rates may have been overestimated by parents' reports, poor inhalation techniques, and inaccurate reports regarding the name of drugs and administered doses. Therefore, although our results may provide an overview of the local study population, they do not necessarily represent patients with asthma in general, meaning that data generalization to other populations is limited.

Conclusions

Inadequate symptom control is associated with worse QoL rates in patients with asthma. The same result was not obtained with asthma severity, possibly due to the limited number of patients with severe asthma (n = 1) or the small sample size. In addition, patients with adequate therapeutic adherence were approximately 3 times more likely to have improved QoL rates than patients with nonadherence. Therefore, the use of a questionnaire that assesses QoL in patients with asthma and adequate clinical follow-up may reveal the real impact of the disease on the lives of these patients and their families. New therapeutic, behavioral, and environmental strategies may be established for patients to achieve adequate control of the disease and, consequently, improved QoL.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Seasonal changes in *Poaceae* pollen counts in Curitiba, south of Brazil

Mudanças na sazonalidade de polens de Poaceae *em Curitiba*

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ABSTRACT

Background: Allergic diseases affect 10% to 30% of the world population, with pollen as a major trigger. Pollinosis results from sensitization to pollen and is the seasonal form of allergic rhinitis and/or immunoglobulin E (IgE)-mediated allergic asthma. The *Poaceae* family is distributed worldwide and has the largest number of plant genera contributing to pollinosis, as they release large amounts of pollen into the atmosphere. **Objective:** To quantify pollen grains from the *Poaceae* family in the atmosphere of Curitiba, compare the pollen distribution curve with data from the 1980s and 1990s, and classify the daily concentration of grass pollen according to the *National Allergy Bureau* (NAB). Method: A Hirst-type volumetric sampler was placed at approximately 25 meters from the ground. **Results:** The peak of daily total pollen concentration occurred in early August, corresponding to 302 grains/m^3. August also had 8 of the highest daily total pollen concentrations, 7 of which were greater than 200 grains/m^3. *Poaceae* pollen was found throughout the year, with the highest concentration peak of 27 grains/m^3 in August and September. In the 1980s and 1990s, the pollen peaks occurred in November and the pollen season occurred between October and April. In 2018, however, the pollen season started earlier, in August, and the pollen peaks occurred in August and September. **Conclusion:** This study shows a change in the grass pollen season. Although the 2 peaks of *Poaceae* pollen dispersion have repeated over the years, grass pollen is currently observed in other months of the year. Patients with pollen allergy may experience symptoms from allergen exposure outside the previously established grass pollen seasons.

Keywords: Pollen, seasonal allergic rhinitis, allergic conjunctivitis.

RESUMO

Introdução: Doenças alérgicas afetam de 10 a 30% da população mundial, e polens são frequentes desencadeantes. A polinose é doença decorrente da sensibilização ao pólen e é a forma sazonal da rinite alérgica e/ou asma mediada pela imunoglobulina E (IgE). A família *Poaceae* tem o maior número de gêneros de plantas que contribuem para a polinose, pois liberam alta quantidade de pólen na atmosfera e são largamente distribuídas. **Objetivo:** O presente trabalho quantificou a concentração de polens da família *Poaceae* na atmosfera de Curitiba e comparou a curva de distribuição de polens com os dados das décadas de 1980 e 90. Também classificou a concentração diária de pólen de gramíneas segundo a *National Allergy Bureau* (NAB). **Método:** O equipamento de amostragem foi o captador volumétrico Hirst, instalado a uma altura de aproximadamente 25 metros. **Resultados:** O pico de concentração diária de pólen total ocorreu no começo do mês de agosto, correspondendo a 302 grãos/m^3. O mês de agosto também concentrou oito dos maiores picos diários de pólen total, sendo sete deles superiores a 200 grãos/m^3. Foi encontrado pólen *Poaceae* ao longo de todo o ano e o maior pico de concentração foi de 27 grãos/m^3 em agosto e setembro. Nas décadas de 80 e 90, os picos de polens foram no mês de novembro e período de polinização entre outubro e abril. Isso não foi observado no ano de 2018, uma vez que a época de polinização das gramíneas se adiantou, com início em agosto, e o pico de concentração foi em de agosto e setembro. **Conclusão:** Este estudo mostra que houve mudança na estação polínica. Os dois picos de dispersão de polens de *Poaceae* se repetem ao longo dos anos, mas têm sido encontrados em outros meses. Pacientes com alergia a polens podem ter sintomas por exposição fora das estações determinadas anteriormente.

Descritores: Pólen, rinite alérgica sazonal, conjuntivite alérgica.

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Introduction

Allergic rhinitis (AR) is an inflammatory reaction of the nasal mucosa characterized by sneezing, nasal itching, rhinorrhea, and nasal congestion in the absence of a cold.[1] Although sometimes mistakenly considered a trivial condition, symptoms can significantly affect one's quality of life and are associated with conditions such as fatigue, headache, cognitive problems, and sleep disturbances, affecting school and work performance.[2] Allergic rhinitis (AR) and allergic conjunctivitis are currently estimated to affect up to 40% of the world's population.[3,4] AR-related ophthalmic symptoms occur in 30-70% of patients and are more commonly triggered by indoor allergens.[5]

Pollen-induced rhinoconjunctivitis represents the most prevalent allergic disease, which is mediated by IgE antibodies and results from the interaction of chemical mediators, cytokines, and adhesion molecules with different cell types, such as endothelial cells, mast cells, lymphocytes, eosinophils, and basophils, among others. The consequence is allergic inflammation and nonspecific hyper-reactivity.[6]

Pollen is the most common airborne allergen and is a frequent trigger of allergic diseases in humans. Pollinosis is the pollen sensitization disease and is considered the acute seasonal form of allergic rhinoconjunctivitis and/or bronchial asthma mediated by IgE antibodies that recurs with the same periodicity.[7,8]

Tests to demonstrate IgE sensitization on the skin in serum or by mucosal provocation and pollen dispersal in the atmosphere are ways to demonstrate the cause of seasonal allergic symptoms. In Brazil, grasses are the main agent of pollinosis and of relatively recent identification.[5,8]

Among the non-native grass species that were introduced to Brazil by European immigrants is ryegrass (*Lolium multiflorum*), a species that has adapted very well to the Southern Region and can therefore be found growing rampantly across the cities of Brazil.[9] According to skin tests performed in pollinosis patients with extracts of different grass species, *Lolium multiflorum* was the species that caused the most allergic reactions; therefore, it is considered the main grass species causing pollinosis.[9-12]

The *Poaceae* family, more commonly called grasses, comprises 668 genera and approximately 10,000 species. In Brazil, about 1,500 species are recorded in the *Poaceae* family.[13]

Since the grass family is large, it was divided into subfamilies and tribes. The subfamilies that comprise 90% of the grass species and 95% of the immunologically relevant species are the subfamilies *Chloridoideae*, *Pooideae*, and *Panicoideae*.[14]

Despite the extensive distribution of grasses in the city of Curitiba, other anemophilous species have a large participation in the pollen concentration in the city's atmosphere along the year, a fact also observed in the municipality of Caxias do Sul, where *Poaceae* corresponded to 12% of the total pollen (TP).[15]

Studies in other countries have shown a wide range in the percentage of grass pollen. In Montevideo, Uruguay, *Poaceae* contributed 47% to 2013-2014 total pollen;[16] in San Carlos de Bariloche, Argentina, grasses contributed on average 6% to TP;[17] and in the city of Porto, Portugal, it reached 8% of total TP.[18]

Historically pollen sampling was done by the gravimetric method using the Durham sampler, with pollens recorded in an area of 1 cm^2. From this count, in 1981 and 1982 it was possible to observe two annual peaks of grass pollen concentration in Curitiba, the highest occurring in the second and third week of November and reaching 117 grains/cm^2, and a lower concentration peak (48 grains/cm^2) in March.[8] The most used method today is the volumetric method, in which pollen counts are expressed in number of grains per m^3 of air.[14]

The prevalence of pollinosis has increased in subtropical regions with well-defined seasons.[18-21] Deforestation associated with the climate of the southern states of Brazil and the introduction of non-native grass species have probably enabled the spread of *Poaceae* grasses in these regions.

Meteorological factors positively or negatively affect plant development, flowering, and pollen concentration in the atmosphere. Relative humidity and temperature influence pollen production and release, as they affect the formation and opening of the anthers for pollen release. Wind speed favors the release of pollen from anemophilous plants but dilutes the pollen concentration in the atmosphere. Finally, precipitation positively influences the concentration of pollen in the atmosphere if it occurs during plant growth since it generally increases pollen production in the plant. However, if precipitation occurs when pollen has already been released into the air, the influence is negative by washing out the biogenic particles.[21]

Air pollution and global warming stimulate plants to develop more, with higher pollen production and

higher allergen content; pollination occurs earlier and is longer and more intense. As a consequence, there will be more pollen allergy sufferers, new sensitizations, more intense symptoms, and earlier onset of symptoms.[11,20,21]

With the occurrence of environmental and phenological changes, it has become necessary to update, by volumetric method, the concentration of grass pollens in our city.

Methods

The sampling site chosen was the terrace of the Administration Building of the Polytechnic Center of the Universidade Federal do Paraná (UFPR), in Curitiba. The sampler was positioned at a height of approximately 25 meters from the ground. The sampling equipment was the Hirst-type volumetric sampler, SporeWatch Spore Sampler, most commonly used for monitoring and counting pollen around the world[14] (Figure 1).

Externally, the sampler is composed of a wind vane that guides the hole in the direction of the prevailing wind, a protection on top against precipitation, and a base for attachment to the terrace surface. Internally, the sampler has a drum, which is covered with polyester tape and fixed in such a way as to allow it to rotate at a speed of 2 mm/h for 7 consecutive days. The sampling period occurred between the months of January and December 2018, in which approximately 40 weeks were sampled.

The material for particle adhesion was gelatin containing 20% glycerol, 5% agar-agar gelatin, and 0.5% phenol in distilled water for 100 mL spread evenly over the tape with the aid of a pipette. After the gelatin had dried on the tape, it was fixed on the drum of the sampling apparatus with a double-sided tape.

We used Melinex polyester tape 19 mm wide and cut to 48 mm, each corresponding to one day of sampling. Each piece was fixed on a glass slide and stained with basic fuchsin solution for analysis under a Nikon Eclipse E200 optical microscope at 400x magnification.

Morphologically similar grass pollens and pollens from other plants were identified and counted in number of grains/m^3 of air. The intensity of pollen dispersal followed the classification of the National Allergy Bureau (NAB), which is part of the American Academy of Allergy Asthma & Immunology.[22]

Figure 1
Hirst-type, SporeWatch Sampler

A total of 222 days were sampled in the year 2018, corresponding to 60% of the year. All months are represented, and the days without samples are related to technical problems with the sampler or the sample, such as rainy days and holidays.

Table 1
Classification of daily grass pollen dispersal according to the National Allergy Bureau (NAB)[22]

Daily concentration (grains/m^3)	Classification
0	Absent
1 – 4	Low
5 – 19	Moderate
20 – 199	High
> 200	Very high

Results

Bioaerosols were counted using two criteria: 1) total pollen (TP), which includes *Poaceae*; 2) pollen from the *Poaceae* family.

The highest daily concentration of total pollen recorded occurred at the beginning of August, corresponding to 302 grains/m^3. The month of August had eight of the highest daily peaks of total pollen concentration, seven of them higher than 200 grains/m^3. The highest percentage of grasses occurred in March, reaching 29% in relation to the total pollen, and December with the lowest contribution of *Poaceae* pollens, only 0.9% in relation to the TP.

Of all the days sampled in 2018, only 12 did not contain any pollen particles, among which five days were in May and four days were in June. *Poaceae* pollen was found across the year and the highest daily *Poaceae* concentration was 27 grains/m^3 in August and September. The second highest peak was 23 grains/m^3 and occurred on 1 day in the months of February, March, April, and October.

Among the days sampled, 21 days had *Poaceae* concentration higher than 10 grains/m^3 and six days, higher than 20 grains/m^3. In 54% of the samples, corresponding to 120 days of those sampled, no *Poaceae* pollen was observed (Figure 2).

Discussion

This study showed that the distribution of total pollen and *Poaceae* occurred throughout the year, although in varying concentrations. The contribution of *Poaceae* to the total pollen concentration in Curitiba on the annual average was approximately 10% of the sampled pollens. On six days spread over the year, counts were within the limits considered high by NAB.[22]

Despite the extensive distribution of grasses in the city of Curitiba, other anemophilous species have a large participation in the pollen concentration in the city air throughout the year, a fact also observed in the municipality of Caxias do Sul, where *Poaceae* corresponded to 12% of the total pollen.[14]

The first pollen count in the city of Curitiba occurred in 1944 for seven consecutive months, showing that the pollination season of grasses occurred between the months of May and June.[23] The second pollen count was performed in the months of February to August 1960; however, no pollination season of grasses was observed, only for *Cupressaceae*.[24]

It is estimated that pollinosis in the South of the country emerged between the 1970s and 1980s, based on the observation of seasonal allergic rhinoconjunctivitis with intense sensitization to allergic

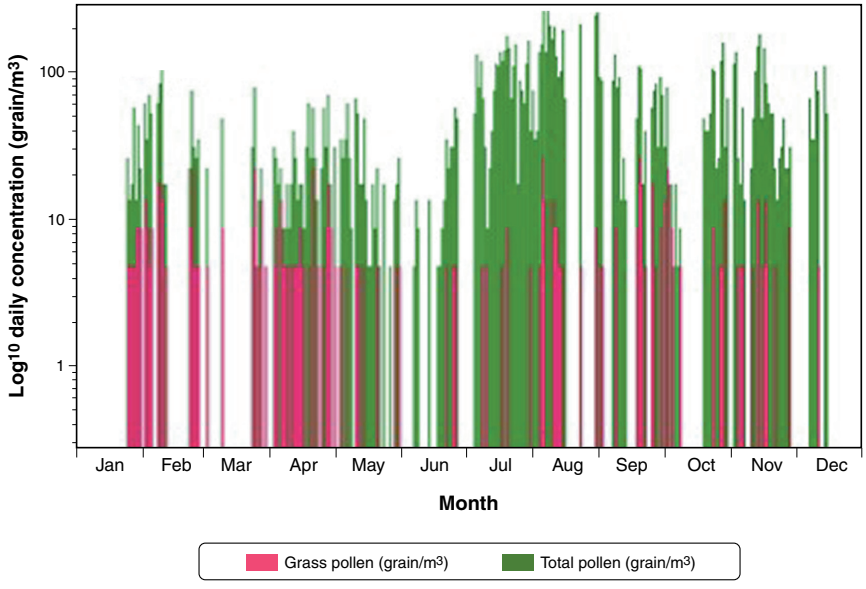

Figure 2
Daily concentration of grass pollen grains (pink) and total pollen (green)

tests with extracts of different grass species, in the city of Curitiba, until then considered an exception in Brazil. Because they occur in the spring months and not in May/June as shown in previous studies, it motivated sampling of airborne pollens in the years 1981/1982, to verify the pollen season of grasses.[5,10,11]

The collection of pollen was done by the gravimetric method using the Durham sampler and the pollen was counted in an area of 1 cm^2. From the results, it was possible to observe two annual peaks of grass pollen concentration, the highest occurring in the second to third week of November and reaching 114 grains/cm^2, and a lower peak of concentration in the month of March and April.

Sampling with the Durham gravimetric sampler was repeated 10 years later in 1991 and it was observed that the peak of grass pollen counts occurred in the second week of November, with 105 pollen grains/cm^2, confirming the spring seasonality and showing that the intensity of grass pollen dispersal had increased in the city of Curitiba.[7,20,21]

The study of pollen concentration in the Southern Region and the relationship with allergic diseases is of high relevance in the context of population health in Brazil. In the present study, it was possible to establish a pollination pattern for *Poaceae* throughout the year in Curitiba. The months between August and April presented the highest concentrations and the total pollen from this period corresponded to approximately 91% of the total grass pollen sampled. The months from May to July had the lowest concentrations and accounted for only 9% of the total *Poaceae* pollen.[8]

In 1982, the highest peak concentration of *Poaceae* occurred in November, followed by smaller peaks in March and January, and near-zero concentrations between the months of July, August, and September.[8] The repeat study in 1991 showed that the peak atmospheric dispersal of grass pollen occurred two weeks earlier, but still in November.[10,11]

In the present study, however, it was observed that the grass pollination season began earlier, in the month of August, but the end of grass pollination remained in the month of April. Therefore, for the year 2018, 36 years after the first collection from Rosario Filho, the grass pollination season was extended for two more months, with the peak concentration also being shifted to the months of August and September. This phenomenon was also noted in Italy, in which grass pollination was measured over 33 years and it was noted that the onset of pollination decreased by -0.4 days/year, with no significant change in the end date of pollination.[9]

Several long-term research studies around the world have studied the correlations between climate change, such as temperature increase, and changes in pollen concentrations in the atmosphere obtained over the years. The introduction of non-native grass species, deforestation, and anthropogenic climate change have likely enabled the spread of *Poaceae* grasses in southern Brazil and the emergence of pollen allergy in these regions.[5,7,20] A recent study on the subject found evidence that among 17 cities in different countries in the Northern hemisphere, 12 had increased annual pollen loads, and in 11 locations the duration of pollination was extended over time, results that demonstrate that the changes are global and independent of latitude.[9,25,26]

Conclusion

The results of this study show the current estimates of pollen concentrations in the capital of the state of Paraná. Therefore, with such data the present research aimed to enable the planning, forecasting, and development of prevention measures to mitigate allergic diseases caused by grasses, the main source of pollinosis around the world.

A limitation of airborne pollen sampling is that it does not allow identification of which species are predominant and at what time of year, because grass pollens are morphologically identical. However, for the clinician this is important, once *Cynodon dactylon* is a species with a wide distribution throughout Brazil and with an allergic sensitization rate similar to *Lolium spp*.

This work should be complemented with further sampling throughout the year in Curitiba to observe whether earlier pollination and a longer distribution and at two concentration peaks, are prevailing. These changes in pollen dispersal serve to alert allergy sufferers in southern Brazil to the possibility of symptoms occurring earlier and longer than previously demonstrated in those sensitized to grass pollen.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Assessment of asthma treatment adherence in children: the influence of specialized care

Avaliação da adesão ao tratamento da asma em crianças: a influência do atendimento especializado

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ABSTRACT

Background: Asthma is the most common chronic disease in childhood. Disease control is challenging but critical to prevent severe exacerbations and long-term damage. Studies in adults have shown that poor adherence to medication and environmental control practices has an impact on disease control. **Objective:** To determine pediatric asthma treatment adherence and associate it with disease control and other clinical variables. **Methods:** This was a cross-sectional observational study of 104 patients with asthma followed up at the Pediatric Allergy, Immunology and Pulmonology Service of the Hospital de Clínicas Complex of the Federal University of Paraná, south of Brazil. Participants were interviewed using questionnaires about medication adherence, environmental control, and popular myths about asthma. **Results:** There was a positive correlation between patients who believed in 1 or more myths about asthma and poorer medication adherence (p=0.025). There was also a significant association between good medication adherence and total asthma control (p=0.038) measured by the 25-point Asthma Control Test. Good and excellent adherence to environmental control practices was reported by 51% of respondents. **Conclusion:** Medication adherence and environmental control were satisfactory in the population of asthmatic children from a specialized outpatient clinic. Popular beliefs influenced adherence and asthma control in these patients. The findings highlight the importance of assertive communication between physicians and patients, as well as of pediatric asthma education programs.

Keywords: Asthma, child, drug therapy, treatment adherence and compliance.

RESUMO

Introdução: A asma é a doença crônica mais prevalente na infância. O controle da doença é desafiador, porém fundamental para evitar exacerbações graves e danos em longo prazo. Estudos em adultos já mostraram que a baixa adesão medicamentosa, bem como aos cuidados do ambiente, impactam no controle da doença. **Objetivo:** Conhecer a adesão ao tratamento da asma na população pediátrica e associá-lo ao controle da doença e outras variáveis clínicas. **Métodos:** Trata-se de um estudo observacional transversal onde foram incluídos 104 pacientes com asma, acompanhados no Serviço de Alergia, Imunologia e Pneumologia Pediátrica do Complexo Hospital de Clínicas da Universidade Federal do Paraná. Foram realizadas entrevistas com base em questionários sobre adesão ao uso de medicação, controle ambiental e crenças populares sobre a asma. **Resultados:** Foi possível identificar uma correlação positiva entre pacientes que acreditavam em um ou mais mitos sobre a asma e pior adesão ao uso da medicação (p = 0,025). Também foi possível identificar uma relação significativa, entre uma boa adesão à medicação e o controle total da asma (p = 0,038) medido pelo *Asthma Control Test* (ACT) de 25 pontos. Cinquenta e um por cento dos participantes entrevistados relatou boa e ótima adesão ao controle de ambiente. **Conclusão:** A adesão e o controle de ambiente avaliados foram satisfatórios na população de crianças asmáticas de um ambulatório de referência. As crenças populares mostraram influência na adesão e no controle da asma dos pacientes entrevistados. Os achados reforçam a importância da comunicação assertiva entre médico e paciente, bem como do papel da educação da asma também voltada para a população pediátrica.

Descritores: Asma, criança, tratamento farmacológico, adesão à medicação.

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Introduction

Asthma is a heterogeneous, multifactorial, and highly prevalent disease. It is characterized as chronic inflammation of the airways and presents with recurrent respiratory symptoms such as wheezing, cough, chest tightness, and shortness of breath.[1] As in other chronic diseases, adequate treatment requires following pharmacological and non-pharmacological recommendations in the long term, which requires discipline by the patient and a good relationship with the medical team.[1,2]

The increased prevalence of chronic non-communicable diseases around the world draws attention to a relevant problem, namely poor adherence to drug treatment.[3] In the pediatric population there are special situations that influence treatment adherence, such as the fact that children, especially preschoolers and schoolchildren, depend on an adult to take care of them, who is not always able to adequately follow medical recommendations.[4]

Misinformation, popular myths, and beliefs can directly contribute to the number of exacerbations, low adherence to the proposed treatment, and the consequent increase in the number of patients who seek medical services and use health care.[5] Another major factor is environmental control, defined as the set of measures to reduce the number of allergens and other substances that are harmful to the airways. Environmental control is one aspect of the non-pharmacological treatment of asthma, and neglecting this practice can lead to a lack of control and exacerbations of the disease.[6]

In recent years, instruments have been created to facilitate the assessment of treatment adherence for chronic diseases. The MARS (Medicine Adherence Rate Scale) is a questionnaire with significant reliability and reproducibility, validated for use in non-specific chronic diseases and translated into Portuguese.[7,8]

The questionnaire comes in two versions, with 10 questions (original version) and with 5 questions, MARS-5, with proven efficiency in determining the degree of adherence.[7,8]

A set of measures that include adequate environmental control, adherence to the prescribed treatment, and the correct use of the inhaler device is expected to optimize asthma control in the pediatric population as well. Therefore, the scarcity of studies quantifying these aspects in the pediatric population was the motivation for developing the present study.

Method

Participants

This is an observational, cross-sectional study. Participants included patients who attended the Pediatric Allergy, Immunology, and Pulmonology Outpatient Clinic of the Complex of the Hospital de Clínicas Universidade Federal do Paraná (CHC).

The inclusion criteria were children diagnosed with asthma, aged between 2 and 14 years, who used continuous medication, were under regular monitoring for at least 6 months, where both the caregivers and the children themselves agreed to participate. The participants whose caregivers reported not knowing about the treatment used, or data on the environmental conditions of the home, were excluded.

Procedures

Patients were approached by the research team at the outpatient clinic, after their scheduled medical appointment. In the outpatient clinic itself, the researchers explained and collected the signature of the caregivers on the Informed Consent Form (ICF) and of the adolescents on the Informed Agreement Form (IAF). The questionnaires were applied to the caregivers when it came to schoolchildren and, in the case of adolescents to the patients themselves, with complementation of the caregivers' answers, if necessary. In this case, if there were divergent answers, they were excluded from the analysis.

During the outpatient clinic visits, we also tested the technique of inhaled medication in practice, classifying it as correct, partially correct (only one error), or incorrect (more than one error).

The study was approved by the Research Ethics Committee of the Hospital de Clínicas da Universidade Federal do Paraná, under approval number 29628220.4.0000.0096.

Instruments

The interviews consisted of the administration of 3 questionnaires: The first about "Environmental control recommendations to be followed in asthma treatment" (Appendix 1),[6] with 15 questions on a Likert scale, with answers "I always do it, I do it sometimes and I never do it"; then, about "Myths and truths about asthma" (Appendix 2),[4] with 6 questions containing simple "yes and no" answers; and, finally, the MARS-5 questionnaire (Medication Adherence Rating Scale

- Appendix 3)[7] that includes 5 questions on a Likert scale, with the answers: "Never, rarely, sometimes, often or always."

The MARS-5 scale, a shorter form of the MARS-10 scale, comprises items that describe some non-compliant behaviors, formulated in a non-threatening and non-judgmental way, with a response scale that allows categorization of patients into "adherence dimensions" and not just based on a dichotomous "yes/no" or "high/low" response, providing greater detail and differentiation between individuals.[8]

In order to evaluate asthma control in the 30 days before the consultation, we used the ACT (Asthma Control Test),[9] which includes 5 questions, with scores ranging from 5 to 25 points. Total control is considered when the score is 25, controlled asthma when the score is between 25 and 20 points, and uncontrolled asthma when the sum is below 20 points.

In addition, data on asthma severity classification, values of serum levels of total IgE, eosinophils, and prick test results were obtained from medical records.

The diagnosis of asthma, as well as the classification of asthma severity, were based on criteria described by the Global Initiative for Asthma – GINA,[1] applied in the first visit and reviewed at each scheduled outpatient visit. Moderate/severe asthma meant it required an additional step in the treatment, besides those described in steps 1 and 2 for the age group.[1] All laboratory tests were conducted in the Clinical Analysis Laboratory of the CHC, the presence of eosinophils above 400 was considered peripheral eosinophilia, while high IgE meant the values were above 150 kU/L.[10]

The immediate reading allergy skin test by puncture is routinely performed in the service and the allergens tested include positive control (histamine), *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Blatella germanica*, *Canis familiaris*, *Felis domesticus*, *Lolium multiflorum*, and negative control (saline solution at 0.9%). It is considered positive, proving sensitization to a particular allergen, if it shows a reaction with the presence of a papule with a diameter greater than or equal to 3 mm, without considering the area of erythema, and when the negative control does not show a reaction.[11]

Results

Ninety-eight children and adolescents with asthma were included. There was a predominance of boys (68%), and the majority of the sample was composed of schoolchildren (73%). The mean age was 8.9 years (±3.68). In 84% of the outpatient clinic visits, the mother was the only caregiver present.

The predominant asthma severity was moderate and severe (82%). Sixty-seven percent of the participants used therapy with more than one drug, and in all cases, inhaled corticosteroids were associated with a second choice (long-acting beta 2 and/or another drug). Inhaled corticosteroid + long-acting beta2 was the most frequent therapeutic option. The median serum eosinophilia was 710 cells/mm^3 (70 – 2.311), and the geometric mean IgE was 1.172 kUL/mL. Eighty participants had a positive skin test for at least one of the allergens (81%), and most (72%) were polysensitized (Table 1).

When the questionnaire on environmental control was administered, 44% said they had no control over the use of plush toys in the child's room, 41% said they did not avoid cleaning around the child, and in 36% of the cases, respondents said they smoked rather often at home. When asked about physical activity, 63% reported that the child/adolescent practiced physical activity regularly.

When the theme "Myths and Truths" was explored, 74% of the respondents answered positively on at least one of the six questions, showing that they believed at least one myth/belief about the disease. Twenty-one percent were suspicious about the safety of the inhalation device, 29% reported being afraid of corticosteroid use, and 45% believed that the use of the inhaler can make the patient addicted.

Eighty percent of the respondents showed good adherence to continuous treatment, according to the MARS-5 questionnaire (score greater than or equal to 20 points), with a mean of 21.7 points (±3.68) (Figure 1). The questions "I forget to take my medication" and "I only take my medication if I am feeling sick" were the most frequent questions in the respondents with low scores, determining low adherence.

Eighty-two (83%) showed correct technique in the use of inhaler devices, and incorrect or partially correct use accounted for 17% of the sample.

In the association between adherence to treatment and clinical variables, asthma control, reliance on myths and beliefs, and technique in the use of inhalers, we found that none of the respondents in the group with good adherence to treatment reported fear in the use of the inhaler and those who responded positively to the greatest number of

popular myths and beliefs had lower adherence to treatment according to the MARS-5 questionnaire. Both findings were statistically significant (p = 0.012 and 0.0256, respectively) (Table 2).

There was a positive correlation between total disease control (maximum ACT score) and good treatment adherence (p = 0.038) (Table 2).

Table 1
Frequency description of the respondents' clinical variables (n = 98)

Variables	n (%)
Positive skin test	80 (81%)
Polysensitized	(71%)
Monosensitized	9 (9%)
Asthma severity	
Severe/moderate	(71%)
Mild	21 (22%)
Atopic comorbidities	
None	44 (44%)
Rhinitis	32 (32%)
Rhinoconjunctivitis	14 (14%)
Atopic dermatitis	8 (8%)
Asthma control (ACT)	
Full control (ACT = 25)	18 (19%)
Control (ACT entre 20-24)	60 (61%)
Uncontrolled (ACT < 20)	20 (20%)
Maintenance treatment	
Inhaled corticoid alone	32 (33%)
Inhaled corticoid + associations	66 (67%)
Eosinophils in peripheral blood [median (range)] [a]	710 (70-2311)
Total IgE (geometric mean in kUL/mL) [b]	1172

[a] Number of participants who collected sample for analysis of peripheral blood eosinophils = 67.
[b] Number of participants who collected sample for total IgE analysis = 69.

Discussion

The present study brings an evaluation of the profile of children and adolescents with asthma seen in a specialized outpatient clinic, focusing on the understanding of patients and families about the disease, the degree of confidence in popular beliefs and myths, adherence to environmental control measures, and adherence to pharmacological treatment and level of adequacy of the technique for using inhalation devices.

Chapman et al.[12] emphasize the practice of environmental control measures, valuing the care of household dust, hair and feathers, pollutants, pollens, and other irritants as important in reducing crises in sensitized patients. Kuster et al.[13] suggested measures in the asthmatic child's room, such as the use of protective plastic for the bed and the removal of carpets. Only 3% of our interviewees said they used plastic protection. Other measures, such as avoiding plush in the bedroom and using wool in blankets and coats, were demonstrated by just over half: 56% and 52% respectively, in a population with a high sensitization index (81%), with over 70% being sensitive to more than one aeroallergen tested. Only half (51%) showed excellent or good environmental control, signaling the need for an emphatic, clear, and

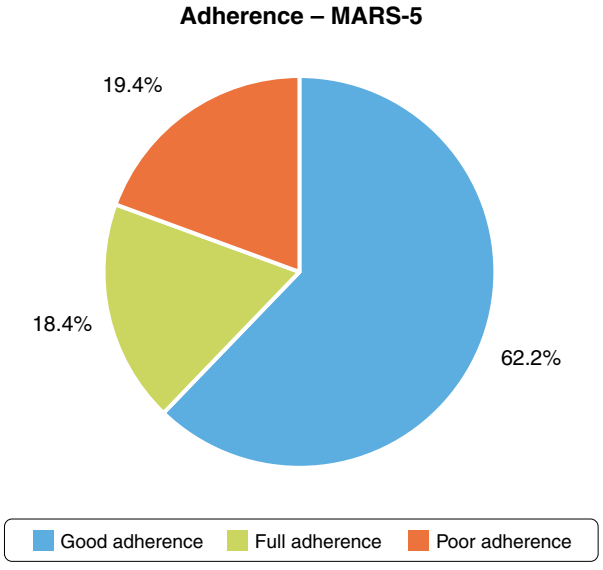

Figure 1
Distribution of MARS-5 questionnaire findings with stratification using the maximum score (25 points) n = 98

Table 2
Adherence to treatment versus clinical variables and popular myths/beliefs (n = 98)

Variables	Good adherence MARS >20	Poor adherence MARS < 20	p[a]
Age range			
Schoolchildren	62 (63%)	7 (8%)	0.06
Adolescents	16 (17%)	12 (12%)	
Asthma control (ACT)			
Full control (ACT = 25)	20 (20%)	0	0.03
Controlled and uncontrolled (ACT < 25)	63 (64%)	(15) 16%	
Inhalation device technique			
Correct	66 (68%)	15 (15%)	
Partially correct	6 (6%)	0	0.19
Incorrect	7 (7%)	4 (4%)	
Myths			
Any fear or concern of using inhalers	0	8 (8%)	0.01
Do you think the inhaler can be addictive?	34 (35%)	9 (10%)	0.45
Concern about using inhaled CTC	20 (21%)	8 (8%)	0.16
Number of myths and beliefs			
None	24 (25%)	1 (1%)	
1	24 (25%)	6 (6%)	
2	18 (19%)	6 (6%)	
3	0	3 (3%)	0.02
4	4 (4%)	1 (1%)	
5	1 (1%)	1 (1%)	
6	1 (1%)	1 (1%)	

[a] Chi-square test.

understandable approach to environmental control measures in follow-up consultations.

In 2016, Roncada et al.[4] studied myths about asthma in a pediatric population in southern Brazil and found that most parents thought that the use of nebulizers was preferable to the inhaler/spray because it was “more natural” and “less harmful” to the child, the same data found by Zhangcols.[14] in 2005. Only 12% of the respondents in this study reported thinking that the nebulizer was better than the metered-dose inhaler (pump), probably because this device has been adopted and encouraged as the choice for children with more severe asthma, with maintenance and relief medications, and, gradually, doubts were resolved and fears were attenuated. In the sample studied, patients with more myths had lower adherence to treatment, which further reinforces the importance of correct guidelines and continuous and periodic clarification about the disease.

Adherence to treatment has been studied in recent years, especially in adult patients with chronic diseases.[4,15,16] Leite & Vasconcellos defined good adherence as the use of at least 80% of the prescribed medications or indicated procedures,[15] also reporting that poor adherence corresponds to a real public health problem worldwide, and is considered an "invisible epidemic."[15]

It is estimated that the worldwide adherence to treatment of chronic diseases is 50%;[4] however, most studies focus on the adult population and on diseases such as hypertension and diabetes mellitus, which are more prevalent than asthma in the pediatric population.[4] The ADERE study[16] was the first in Brazil to analyze the adherence to asthma treatment in different regions of Brazil and showed an adherence rate of 51.9% in adults with a mean age of 44 years. In this study, using the MARS-5 questionnaire as an instrument, we found a treatment adherence rate of 80.6%, higher than that of the general population. The care of the pediatric population is usually enhanced when compared to adults; medications and other measures are administered by the guardians and caregivers, who are usually more concerned when the disease carrier is their children or tutored.[15] Most of the patients included had moderate and severe asthma, which leads to scheduled appointments at shorter intervals and in a specialized outpatient clinic with medical students, residents, and professors, where, as part of the teaching, they spend time explaining the disease, the importance of the regular use of medications, and guiding the technique of using inhaler devices at each visit. It should be noted that the study was developed during the period of the COVID-19 pandemic when parents and children stayed indoors longer. In the same line of thought, the high number (83%) of children and adolescents performing the proper technique of the inhalation devices tested is understood.

Boulet et at.[17] reported instruments used to assess medication adherence in asthma patients, such as self-report, inhaler device weighing, pharmacy dispensing records, and electronic monitoring, and they consider the latter to be the gold standard. The instrument used in this study was a questionnaire that behaves like a self-report, described as a limitation in some studies.[8,17]

Although electronic monitoring of adherence is considered the gold standard method, it is expensive and fails to identify the types of non-adherence (intentional or unintentional), and in certain situations, valid and reliable methods to capture this information, such as patient self-reporting, are recommended.[8]

Children with fully controlled asthma (ACT 25) showed complete adherence to pharmacological treatment determined by MARS-5, corroborating the idea that the correct and regular use of the proposed asthma drugs reflects in good control of the disease in children and adults.

The impacts of uncontrolled asthma on public health in Brazil are enormous. Cardoso et al.[18] studied the repercussions of asthma in Brazil, showing costs of over 168 million dollars between 2008 and 2013 in asthma hospitalizations, with an average of 120,000 asthma hospitalizations in the period. In 2013 alone, there were 2,407 deaths, representing an average of 5 deaths per day.[18] In Brazil, since 2009, there has been a free corticosteroid and short-acting bronchodilator supply program in Health Units and pharmacies registered by the Ministry of Health.[19]

In 2007, Ponte et al.[20] analyzed the impact of a public health policy program on health system costs for asthma patients in the state of Bahia. PROAR (Asthma and Allergic Rhinitis Control Program in Bahia) is a program of assistance, teaching, and research that offers patients with severe asthma free medication, medical and psychological care, pharmaceutical assistance, and asthma education.[20] A reduction in the number of days absent from school and work, emergency room visits, hospitalizations, and use of systemic corticosteroids was observed after one year of the program, and it was estimated that 7,000 emergency room visits and 300 hospitalizations were avoided in the period studied.[20]

Reminder methods in the form of text messages, automated phone calls, and audio-visual reminder devices have been tested to increase medication adherence in patients with chronic diseases, including asthma, with good results on adherence despite not impacting the quality of life and clinical outcomes.[21]

Asthma requires special attention not only because it is the most prevalent chronic disease in pediatrics, but also to avoid exacerbations, hospitalizations, mortality, and loss of quality of life, as well as the consequences of the disease in adult life. Adherence to treatment in the most global sense is a fundamental factor to guarantee all these aspects and should be sought by physicians and the multiprofessional team, patients, and family members.[22]

Asthma education measures should be prioritized and adopted, not only in specialized outpatient clinics but in all services that treat children with asthma, in the public and private spheres, seeking the control of this prevalent disease with great social and economic impact.

Appendix 1

Environmental Control Questionnaire: "Recommendations to be followed in the treatment of asthma"[6]

Answer with "Always, sometimes, or never."

1. Cover the pillow and mattress with plastic material.
2. Not using wool blankets or sweaters.
3. If another person must sleep in the same room, also protect the bed.
4. Not allowing play with rugs or sofa. Avoid plush, fur, or wool toys.
5. Not applying insecticide.
6. Avoid active odors, such as perfume, wax, gasoline, and smoke.
7. Avoid house dust, avoid dusting, sweeping, or tidying the bed in the presence of the child. Clean the room every day.
8. Apply anti-mildew where susceptible.
9. Avoid humid environments and handling objects that have been stored for a long time.
10. Not smoking nearby.
11. Having an outdoor life.
12. Practice sports, especially swimming.
13. Take cold baths.
14. Sleep in a ventilated room.
15. Not making use of a fan.

Appendix 2

Questionnaire on "Myths and truths about asthma"[4]

Answer with "yes or no."

1. Do you have any concerns or fears about using the inhaler/spray as a form of asthma treatment for your child?
2 Do you have any concerns or fears about using inhaled corticosteroids for the treatment of asthma in your child?
3. Do you think that the inhaler/spray can be addictive to people who use it as a form of asthma treatment?
4. Do you use a nebulizer as a form of asthma treatment for your child?
5. Do you consider the use of nebulizer more efficient than the use of "inhaler/spray" to treat your child's asthma?
6. Do you think that the practice of physical activities can help your child's asthma treatment?

Appendix 3

Questionnaire: "Medication Adherence Report Scale" – MARS-5[7]

Answer "always, almost always, sometimes, rarely, never", where:

always = 1, almost always = 2, sometimes = 3, rarely = 4, and never = 5.

Full adherence = 25 points.
Good adherence > 20 points.
Low adherence < 20 points.

1. Have you ever forgotten to take your medication?
2. Are you sometimes careless in taking your medication?
3. When you feel better, do you sometimes stop taking your medication?
4. Occasionally, if you feel worse when you take your medication, do you stop taking it?
5. Do I only take my medication when I feel sick?

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Anaphylaxis during the first year of life of infants with cow's milk protein allergy

Anafilaxia durante o primeiro ano de vida em pacientes com alergia à proteína do leite de vaca

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ABSTRACT

Objective: To describe the early manifestations of anaphylaxis in infants with cow's milk protein allergy (CMPA) and the therapeutic approach. **Method:** In this cross-sectional observational study, we retrospectively reviewed the medical records of patients with CMPA treated at the Institute for Children and Adolescents of Hospital das Clínicas, University of São Paulo Medical School, from 1990 to 2015. Patients who developed allergic symptoms during the first year of life and had a diagnosis of anaphylaxis were compared with allergic patients without anaphylaxis triggered by cow's milk. Patients were characterized according to epidemiological features, type of symptoms, and treatment received. Data were analyzed using GraphPad software. Associations between categories were assessed by Fisher's exact test, and groups were compared by the Mann-Whitney test. Results with $p<0.05$ were considered statistically significant. **Results:** Of 120 infants evaluated (68 male: 52 female), 85 (70.83%) met the World Allergy Organization criteria for anaphylaxis. Most infants had cutaneous manifestations of immunoglobulin E (IgE)-mediated allergy (n=102, 85%). In those with a diagnosis of anaphylaxis, the main manifestations were urticaria (n=39, 45.8%), vomiting (n=36, 42.3%), and dyspnea (n=19, 22.3%). Anaphylaxis recurred in 41 patients (34.16%). Epinephrine (45%) and antihistamines (63.3%) were the most used drugs. Six patients (7%) with a diagnosis of anaphylaxis received no treatment. **Conclusion:** Anaphylaxis during the first year of life showed clinical features similar to those of older pediatric patients, but the rates of episode recurrence and undertreatment are still high. More education strategies need to be developed.

Keywords: Anaphylaxis, milk hypersensitivity, food hypersensitivity.

RESUMO

Objetivo: Descrever as manifestações de anafilaxia precoce em lactentes com alergia à proteína do leite de vaca (APLV) e descrever as condutas terapêuticas utilizadas. **Método:** Estudo observacional transversal retrospectivo que analisou pacientes com APLV atendidos no Instituto da Criança e do Adolescente do Hospital das Clínicas da FMUSP, entre 1990-2015, que apresentaram sintomas de alergia no primeiro ano de vida, com diagnóstico de anafilaxia, comparados a pacientes alérgicos sem anafilaxia desencadeada por ingestão de leite de vaca. Os pacientes foram caracterizados de maneira epidemiológica, tipo de sintoma apresentado e tratamento realizado. Os dados foram analisados no programa estatístico GraphPad Software Inc. Para avaliar a associação entre categorias, foi utilizado o Teste Exato de Fisher, e para comparações entre grupos, o Teste de Mann Whitney. Os resultados de $p < 0,05$ foram considerados significativos. **Resultados:** De um total de 120 crianças avaliadas (68 M:52 F), 85 (70,83%) lactentes preencheram os critérios da *World Allergy Organization* (WAO) para anafilaxia. As manifestações de alergia IgE mediada foram prioritariamente cutâneas [102 (85%)]. Nos pacientes com diagnóstico de anafilaxia, as principais manifestações foram urticária [39 (45,8%)], vômito [36 (42,3%)] e dispneia [19 (22,3%)]. A recorrência do episódio de anafilaxia ocorreu em 41 (34,16%) pacientes. A adrenalina (45%) e o anti-histamínico (63,3%) foram os medicamentos mais utilizados. Observa-se também que 6 (7%) pacientes com diagnóstico de anafilaxia não receberam nenhum tratamento. **Conclusão:** Anafilaxia no primeiro ano de idade apresenta quadro clínico semelhante aos pacientes mais velhos, mas ainda há elevada taxa de recorrência de episódios e subtratamento. Mais estratégias de educação precisam ser desenvolvidas.

Descritores: Anafilaxia, hipersensibilidade ao leite, hipersensibilidade alimentar.

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Introduction

Food allergy is a major public health concern, affecting at least 1-2% of children and adults.[1,2] It is characterized by an adverse reaction to food that compromises the immune system involving IgE-mediated reactions, cell-mediated mechanisms (non-IgE mediated), or both (mixed mechanisms), as in eosinophilic esophagitis or atopic dermatitis.[2] In IgE-mediated reactions, symptoms occur within two hours of ingestion of the food, and histamine release is the main result of IgE action. Patients with IgE-mediated allergy have symptoms in various systems, which differs from non-IgE-mediated allergies, where gastrointestinal symptoms predominate. Urticaria, angioedema, vomiting, and bronchospasm are some of the symptoms reported by patients with IgE-mediated allergy, but anaphylaxis is the most feared manifestation.[2]

Anaphylaxis is an acute systemic or generalized life-threatening event. Several systems may be involved, but it is vascular instability or respiratory compromise that confer greater severity to the anaphylactic reaction.[2,3] The increasing prevalence of allergic diseases has also resulted in an increase in the records of anaphylaxis.[4]

Foods are important causes of severe reaction triggers in adults, but even more so in children.[5] In American studies, peanuts and tree nuts are the main causes of anaphylaxis, but milk ranks third.[5] In Brazil, milk is the major food allergen, and although there are no prevalence studies on food allergy, two national studies involving presumed prevalence or office-based surveys confirm this premise.[6,7] A national study found cow's milk allergy in children to be more prevalent by non-IgE mechanism, but this is a result conflicting with the literature, so this diagnostic hypothesis should be considered mainly according to the patient's clinical condition.[8,9]

It is known that patients with CMPA present symptoms early, mostly in the first year of life, and in this setting, the identification of anaphylaxis can be more difficult, which may impair the outcome. It is known that early recognition of the disease is a crucial factor for initiating the therapeutic approach, which includes the administration of intramuscular adrenaline, an important measure to minimize the risk of death in these patients. There is a significant shortage of studies evaluating this particular age group, especially if we consider Latin America.[10] It is important to recognize the characteristics of anaphylaxis in the first year of life, the symptoms presented, and the evaluation of the therapy applied. In this context, we proposed this study, whose aim was to describe the manifestations of anaphylaxis in the first year of life in infants with CMPA and to characterize this population by comparing them to patients with the same allergy who did not present with anaphylaxis. A secondary objective was to also describe the therapeutic approaches to anaphylaxis in this age group.

Method

This was a retrospective cross-sectional observational study that analyzed the records diagnosed with CMPA that started their symptoms in the first year of life seen at the Child Institute (Instituto da Criança) at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (ICR-HC/FMUSP), from 1990 to 2015. This study was approved by the Research Ethics Committee of the Universidade Anhembi Morumbi under number 46370315.6.0000.5492.

Study population

We conducted a retrospective study that included data catalogued in the digital archive of the ICR-HC/FMUSP of patients who presented the following inclusion criteria:

– onset of symptoms of IgE-mediated CMPA before one year of age;
– diagnosis confirmed by suggestive clinical history associated with positive specific IgE to CM and/or fractions (specific serum IgE ≥ 0.35 kUA/L or positive prick test ≥ 3 mm, considered negative control 0) and clinical reproducibility evidenced on oral provocation test (OPT) with pure CM or Clinical history of anaphylaxis in the past 12 months after exposure to CM, associated with the presence of specific IgE to CM and/or fractions, even without performing OPT.

Patients whose data on the medical records were insufficient for analysis were excluded.

The data collected allowed the epidemiological and clinical characterization of the population using a protocol that includes a description of sex, date of symptom onset, presence of atopic diseases, diagnosis of anaphylaxis, description of manifested symptoms, affected systems, treatment introduced, and recurrence of the anaphylactic condition. The

patients were separated into two groups: those who presented characteristic symptoms of anaphylaxis and those who did not.

Patient manifestations were named anaphylactic when they met any of the three criteria proposed by the World Allergy Organization for diagnosing anaphylaxis (WAO - 2011).[11]

The data were analyzed using GraphPad Prism version 8.0, available online at the website http://www.graphpad.com/quickcalcs/index.com. Numerical variables were described as mean, standard deviation, and 95% confidence interval (95%CI), and categorical variables as percentages or proportions. Continuous variables were expressed as median with their minimum and maximum values.

The Chi-square or Fisher's Exact tests were used to assess the association between categories, and comparison between groups was performed by either the Mann-Whitney or Kruskal-Wallis Test according to the number of groups. Standard error, 95% confidence interval, and statistical significance were reported. Significance was set at $p < 5\%$.

Results

We reviewed 120 medical records of patients who presented with symptoms of cow's milk protein allergy before one year of age. Among these infants, 52 (43.5%) were girls, and 68 (56.7%), boys. By carefully evaluating the diagnosis of the 120 patients, 85 (70.83%) met the criteria for anaphylaxis when analyzing the symptoms presented in the first episode of CMPA, while 35 (29.17%) did not meet the criteria. Both groups were named with acronyms for ease of mention; the group diagnosed with anaphylaxis was named "ANA" and the undiagnosed group "N-ANA." Although this study had the limitations inherent in a retrospective study, it was noteworthy that all symptoms reported by parents and the diagnoses of anaphylaxis were reviewed according to the proposed criteria.

The clinical and epidemiological characteristics are presented in Table 1. No differences were observed regarding sex and age of symptom onset (Fisher's Exact Test). The involvement by symptom system was primarily cutaneous, affecting 102 (85%) infants, followed by gastrointestinal symptoms in 58 (48.3%), respiratory symptoms in 38 (31.6%), and cardiovascular/systemic symptoms in 13 (10.8%) (Table 1).

In patients diagnosed with anaphylaxis, the main manifestations were urticaria [39 (45.8%)], vomiting [36 (42.3%)], and dyspnea [19 (22.3%)]. In patients who did not have a diagnosis of anaphylaxis, the main manifestations were urticaria [7 (20%)], perilabial hyperemia [7 (20%)], and vomiting [9 (25.7%)] (Table 1).

Recurrence of anaphylaxis episodes occurred in 41 (34.16%) patients, who were known to have been previously diagnosed with anaphylaxis. Evaluation of

Table 1
Treatment used in the anaphylactic episode in children under one year of age compared with treatment performed in patients who did not present anaphylaxis

Treatment of first episode referred to as anaphylactic	Total (n = 120) n (%)	ANA (n = 85) n (%)	N-ANA (n = 35) n (%)
Adrenaline	54 / 45	52 / 61.1	2 / 5.7
Antihistamine	76 / 63.3	44 / 51.7	32 / 91.4
Corticoid	44 / 36.6	20 / 23.5	24 / 68.5
None	9 / 7.5	6 / 7	3 / 8.6
Inhaled beta-2	4 / 3.3	4 / 4.7	–

anaphylaxis recurrence was performed only in patients diagnosed with anaphylaxis under one year old.

Among the patients who had not been previously diagnosed with anaphylaxis, 9 had their first manifestation after the first year of life, and it was not possible to precisely define the number of episodes that occurred by analysis of the medical records, only their existence (Table 1).

Regarding associated atopic diseases throughout the follow-up, rhinitis was the most prevalent, with 50 (41.7%) patients diagnosed, followed by asthma, with 48 (40%), and atopic dermatitis, with 25 (20.8%), and there were no significant differences between the two groups (Table 1).

Regarding the treatment of anaphylaxis (Table 2), considering the entire sample (n = 120), we observed that adrenaline (45%) and antihistamine (63.3%) were the most prevalent drugs. In patients diagnosed with anaphylaxis, this pattern was repeated [adrenaline (61.1%) and antihistamine (51.7%)], and in patients without a diagnosis of anaphylaxis, the most prevalent treatments were antihistamine (91.4%) and corticoid (68.5%). It was also observed that six (7%) patients diagnosed with anaphylaxis did not receive any treatment. In contrast, two (5.7%) patients without a diagnosis of anaphylaxis received adrenaline.

Fisher's Exact Test was used to compare ANA and N-ANA pairs for respiratory (p = 0.6832) and gastrointestinal (p = 0.1098) manifestations, with no significant p-value. On the other hand, when assessing skin (p = 0.01) and cardiovascular (p = 0.003) manifestations there was statistical significance.

The recurrence rate of anaphylaxis was high, 41/120 patients had anaphylaxis and recurred later. Nine patients did not have anaphylaxis before 1 year and after this age presented cow's milk anaphylaxis. There was no correlation between early anaphylaxis and recurrence of anaphylaxis (p = 0.2928). A high prevalence of other, unrelated to the presence of anaphylaxis before the first year of life, was observed.

Discussion

The major contribution of this study was to better understand the manifestations of anaphylaxis in young infants, particularly in the first year of life. There are few studies in the literature that specifically evaluate children in this age group. It is known that foods are the main causes of anaphylaxis, and cow's milk proteins are among the most frequent allergy triggers.[11,12] The early onset of symptoms is one of the highlights of this study, with reports of symptoms such as erythematous plaques and vomiting as early as the first day of life. These manifestations reinforce the possibility of intrauterine sensitization and highlight the offer of polymeric formula in the nursery as a possible trigger of symptoms. The median onset of symptoms in IgE-mediated allergies was quite early (4 months), but there was no distinction in the age of symptom onset between anaphylactic and non-anaphylactic patients. A point for discussion and a limitation of this study is the non-uniformity in the amount of milk ingested by patients in the anaphylactic and non-anaphylactic groups. Since the intakes were casual, it is possible to speculate that patients with anaphylaxis may have ingested larger amounts or more allergenic preparations (unprocessed foods) than patients who did not have anaphylaxis in the first year of life, which is a possible confounding factor. Importantly, the reasons why certain patients with CMPA develop anaphylaxis and others do not are not fully understood. But factors such as fasting, the presence of infections, or the amount of food ingested may be relevant to the outcome of anaphylaxis, and these factors were not evaluated in this study.

Clinical manifestations of IgE-mediated food allergy occurred mainly on the skin in both groups, but significantly more frequently among the anaphylactic patients. The frequency of cutaneous manifestations in this group was similar to those described in the older populations. It is known that cutaneous manifestations are usually the most frequent, approximately 80%, in children diagnosed with anaphylaxis, regardless of the triggering agents.[13-15] Right after the skin, the gastrointestinal system seems to be the most affected, affecting almost half of the patients. In this study, respiratory symptoms were much more frequent in patients with anaphylaxis, being described in isolation in a minority of cases. It is worth noting that isolated respiratory manifestations are even the least frequent among patients with IgE-mediated allergy, but they are not negligible. However, it is always worth noting that the respiratory symptoms associated with IgE-mediated food allergy occur about two hours after the administration of the food, and do not remain continuous, as do other causes of wheezing.[13-15]

In our study, there was no relationship between the occurrence of anaphylaxis and the development of other atopic diseases, especially atopic dermatitis. The association between atopic dermatitis and anaphylaxis

Table 2
Clinical-epidemiological characteristics of the 120 patients with CMPA manifestations in the first year of life (description of symptoms according to data in the medical chart)

Characteristics	Total N (%)	ANA (n = 85) N (%)	N-ANA (n = 35) N (%)	p
Sex				
Boys	68 (56.6)	47 (55.2)	21 (60)	0.689
Age at symptom onset median in days (min-max.)	120 (1-365)	120 (7-365)	120 (1-300)	
Manifestations of anaphylaxis in children under one year of age				
Cardiovascular /systemic symptoms	13 (10.8)	13 (5.2)		NA
Hypotonia	7 (5.8)	7 (8.2)	–	–
Cyanosis	4 (3.3)	4 (4.7)	–	–
Loss of consciousness	1 (0.8)	1 (1.1)	–	–
Intense crying	1 (0.8)	–	1 (2.8)	–
Anaphylactic shock	1 (0.8)	1 (1.1)	–	–
Skin symptoms	102 (85)	78(91,7)	24 (68.5)	0.003
Urticaria	66 (55)	56 (65.8)	10 (2.8)	–
Angioedema	67 (56)	64 (75.2)	3 (0.08)	–
Perilabial hyperemia	11 (9.1)	4 (4.7)	7 (0.2)	–
Perioral papule + facial hyperemia	7 (5.8)	2 (2.3)	5 (0.1)	–
Erythroderma/Rash	7 (5.8)	6 (7)	1 (0.02)	–
Pruritus	5 (4.1)	4 (4.7)	1 (0.02)	–
Respiratory symptoms	38 (31.6)	33 (38.8)	5 (14.2)	0.6832
Dyspnea	21 (17.5)	19 (22.3)	2 (0.05)	–
Wheezing	13 (10.8)	12 (14.1)	1 (0.02)	–
Cough	6 (5)	5 (14.2)	1 (0.02)	–
Runny nose	1 (0.8)	1 (1.1)	–	–
Gastrointestinal symptoms	58 (48.3)	46 (54.1)	12 (34.2)	0.1098
Vomiting	45 (37.5)	36 (42.3)	9 (25.7)	–
Diarrhea	11 (9.1)	8 (9.4)	3 (8.5)	–
Colic	5 (4.1)	3 (3.5)	2 / (5.7)	–
Regurgitation	2 (1.6)	2 (2.3)	–	–
Other anaphylaxis episodes				
Patients with anaphylaxis during the first year who presented other anaphylaxis episodes	41 (34.1)	41 (48.2)	NA	–
First anaphylaxis in > 1 year of age	9 (7.5)	NA	9 (25.7)	–

is a well-known risk factor, comprising about 58% of the cases analyzed in a multicenter study conducted in Italy.[11] However, the result of the present study allows us to argue that although anaphylaxis and atopic dermatitis are strongly correlated, the precocity of anaphylaxis below one year of age is not a greater risk factor. Another risk factor analyzed in this Italian study was sex, with boys being the most affected.[11] This is compatible with our sample, which showed more male patients, but this was not a risk factor for the development of anaphylaxis during the first year of life.

The recurrence of anaphylaxis was another point raised and studied in the present study, reaching a percentage of 34.1% in the general data. We believe that the number of patients included in this study was insufficient to show us a relationship between the previous episode of anaphylaxis and its recurrence; however, it is important to emphasize that the possibility of recurrence exists, as patients who had already been diagnosed with anaphylaxis recurred, showing the importance of guidance for parents in order to avoid recurrence.

The treatment performed during anaphylactic crises was also surveyed, showing inequality in the treatment of anaphylactic symptoms in one-year-olds or younger infants. It is noteworthy that patients with anaphylaxis did not receive proper treatment, but not only that, what is even more alarming is that there were patients who did not even receive any treatment, and fortunately there was no fatal outcome. This reflects the difficulty of physicians in diagnosing anaphylaxis and also a lack of knowledge when it comes to choosing the appropriate medication. All these factors can be further aggravated in children under one year old. The inexperience of parents, pediatricians in some emergency services, fear of using adrenaline, and difficulty in establishing the diagnosis are only some of the factors that can contribute to delayed medication, as also highlighted by Simons et al.[15]

The use of adrenaline as rescue therapy is widespread in other countries, and its use is recommended on a large scale. Since adrenaline is the medication with the best results in an anaphylactic reaction, its use, even in more than one dose, could be better recommended and known by the professionals who work in the first aid team.[16,17] Intramuscular injection of adrenaline is the treatment of choice in anaphylaxis. Its plasma peak reaches high concentrations in a short period of time, bringing almost immediate effects to the patient.[18]

A study in Japan shows that pediatricians are poorly trained and unable to identify an ongoing anaphylactic condition, nor are they trained to properly treat pediatric patients in an anaphylactic crisis, and their deficiencies in management may result in failure to diagnose and prevent recurrences of anaphylaxis.[19]

Since the diagnosis in these patients can be quite difficult given the non-specificity of the symptoms, it is important to properly recognize the infants at risk, the triggering factors, the risk and recurrence factors present in the personal history, and the appropriate treatment.

There are several hypotheses to explain the growth of food allergy in infants, such as the use of antibiotic therapy by pregnant women during the perinatal period and prematurity. The use of antimicrobials would affect the fetal immune response by reducing intestinal tolerance cytokines, such as IL-10 and TGF-β; in prematurity, the immaturity of the gastrointestinal barrier could be related to the breakdown of the intestinal barrier and lower evolution of tolerance.[17] In our sample, it was not possible to collect these data on the perinatal period, and it is not possible to establish relationships.

Anaphylaxis in infants under one year of age is an event that needs to be more widely known, especially with the increasing prevalence of food allergies. Cow's milk stands out as the most frequent food in this age group. Although its manifestations resemble the symptoms in older age groups, there is a large number of children who do not receive appropriate treatment even in emergency services. Increased information and continuing education for family members and physicians in the emergency room can minimize the recurrence of symptoms and allow for more appropriate treatment.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Difficulties in diagnosing allergic rhinitis in infants: a systematic review

Dificuldades do diagnóstico de rinite alérgica em lactentes: revisão sistemática

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ABSTRACT

Background: Allergic rhinitis has been neglected in infants, mainly because the diagnosis is challenging. **Objective:** To identify the methods used to diagnose allergic rhinitis in infants. **Methods:** From April to August 2020, 2 independent reviewers systematically searched Scopus, PubMed/MEDLINE, SciELO, and LILACS databases using the following keywords: allergic rhinitis, diagnosis, and infant. The search considered original studies in English or Spanish involving children aged 0 to 2 years, regardless of publication date. **Results:** A critical analysis of the 5 included studies showed great heterogeneity in the definition of allergic rhinitis in children under 2 years of age. No studies were found that established an index test or gold standard, and there was no comparison between the available diagnostic methods. Because the clinical symptoms of allergic rhinitis in infants are variable and nonspecific and sensitization to aeroallergens is not necessarily clinically significant, making an accurate diagnosis of allergic rhinitis remains difficult in young children. **Conclusion:** Careful medical history and physical examination by the attending physician are essential for the diagnosis of allergic rhinitis in infants, as are the tests to be used for the detection of allergic sensitization, whose results should be correctly interpreted and correlated with the patient's medical history and physical examination.

Keywords: Allergic rhinitis, infant, diagnosis.

RESUMO

Introdução: Rinite alérgica em lactentes é uma condição negligenciada, principalmente pelo seu diagnóstico desafiador. **Objetivo:** O presente estudo propõe identificar os métodos de investigação usados para o diagnóstico de rinite alérgica em lactentes. **Método:** Dois examinadores, de forma independente, realizaram busca sistemática da literatura, de abril a agosto de 2020, utilizando quatro bases de dados: Scopus, PubMed/MEDLINE, SciELO e LILACS. Foram usadas as seguintes palavras-chaves: rinite alérgica, diagnóstico e lactente. Foram pesquisados estudos originais na língua inglesa e espanhola, com crianças de 0 a 2 anos de idade, sem distinção de data de publicação. **Resultados:** Em análise crítica dos cinco estudos selecionados, percebeu-se grande heterogeneidade de definição de rinite alérgica em crianças menores de dois anos. Não foram encontrados estudos que estabeleceram um teste índice e o padrão ouro e não houve comparação entre os métodos diagnósticos disponíveis. A variabilidade e a inespecificidade de sintomas clínicos de rinite alérgica em lactentes, associadas ao fato de que a sensibilização a aeroalérgenos não tem necessariamente significado clínico, representam uma dificuldade para o correto diagnóstico de rinite alérgica em crianças pequenas. **Conclusão:** Para o diagnóstico de rinite alérgica em lactentes, é fundamental que o médico assistente realize cuidadosa anamnese e exame físico, além de testes para detectar sensibilização alérgica com correta interpretação do resultado e correlação com a história clínica e exame físico do paciente.

Descritores: Rinite alérgica, lactente, diagnóstico.

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Introduction

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated disease that causes inflammation of the nasal sinus mucosa and is triggered by exposure to aeroallergens in individuals with a genetic predisposition.[1,2] Common symptoms include nasal congestion, rhinorrhea, sneezing, and itching.[1-3] Studies have reported a prevalence of AR ranging from 0% to 48% in infants, and this is not only due to geographic differences, but also to different criteria and definitions used to diagnose AR in young children.[4] The increase of AR in infants has become a problem, as AR is associated with sleep deprivation, fatigue, lack of concentration and learning difficulties, high medication expenses, and school absenteeism. It may also progress to asthma or exacerbate pre-existing asthma.[2,3,5] However, AR in infants is an unnoticed, mistreated, and misunderstood condition. It is neglected in all aspects, mainly because it is difficult to diagnose.[2,6]

It is challenging to diagnose AR in infants, both because of the similarity to upper airway infections, which are frequent in this age group, and the difficulty in performing tests to diagnose its etiology and assessing its subjective symptoms.[2] Infants with AR symptoms should have the following differential diagnoses excluded: cystic fibrosis, choanal atresia or stenosis, foreign body, inborn errors of immunity, and primary ciliary dyskinesia.[1,2,7]

The main international guidelines and the Brazilian consensus on rhinitis[1] consider a comprehensive medical history (clinical history, rhinitis symptoms, personal and family history of atopy), careful physical examination, and proof of allergic sensitization crucial for the diagnosis of AR. Thus, the diagnosis of AR is clinical and associated with identification of the possible causative allergen through skin prick test for immediate hypersensitivity or a serum specific IgE.[1,3,8,9] The Japanese consensus on AR includes a positive nasal eosinophil test.[10]

The present review aims to identify the criteria used to diagnose AR in infants in order to understand the current diagnostic variability, aid clinical practice, and guide future research. The review also aims to foster further research on AR in infants and to encourage the best diagnosis-based treatment for this age group.

Methods

A systematic review was conducted to answer the question "what are the diagnostic criteria available to diagnose AR in infants?". The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD420209565.

A systematic literature search was performed from April to August 2020 using the following keywords and Boolean operators: diagnosis AND allergic AND rhinitis AND infant (Scopus); (("Rhinitis, Allergic" [MeSH]) AND "Diagnosis" [MeSH]) AND "Infant" [MeSH] (PubMed/MEDLINE); rhinitis, allergic AND diagnosis AND infant (SciELO); "Allergic Rhinitis" Infant Diagnosis (LILACS). We searched for original studies in English and Spanish including infants aged 0 to 2 years, regardless of publication date.

The results of the database searches were compiled, and 2 reviewers independently and concurrently screened titles and abstracts. The concordant articles were selected for full-text review, whereas the divergent ones were jointly reviewed, and a third reviewer resolved any discrepancies.

During full-text review, studies that did not provide information about the diagnosis of AR and that did not strictly address children under 2 years of age were excluded. Figure 1 shows the study selection process.

For data extraction, we analyzed methods, participants, clinical setting, definition of AR in the study, testing, and results. Data were extracted with a standardized form and compiled in tables, which allowed us to observe a variety of tests and results.

Results

The systematic review of data on diagnostic criteria for AR in infants was not feasible. No primary studies were found to answer the question about the diagnostic criteria available to diagnose AR in infants.

The studies showed great heterogeneity in the definition of AR in children under 2 years of age. No studies were found that established an index test or gold standard, and there was no comparison between the available diagnostic criteria.

Therefore, the present study proposes a critical analysis of the 5 studies retrieved from the systematic search addressing the diagnosis of AR in infants. Table 1 shows the characteristics of each study.

Herr et al.[11] studied 1850 children in the PARIS birth cohort. AR symptoms (rhinorrhea, nasal obstruction, and sneezing without a cold) were collected through a standard questionnaire directed at

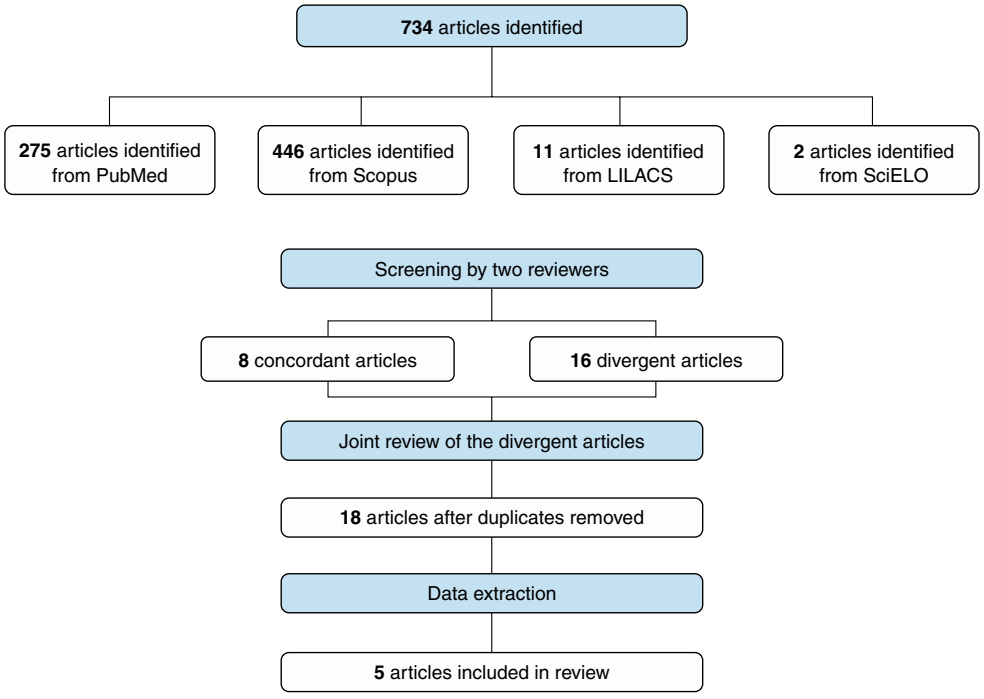

Figure 1
Flowchart of the study selection process

the infants' caregivers. Parental history of allergy and blood markers of atopy (eosinophils ≥ 470 mm^3, IgE ≥ 45 U/mL, and presence of allergen-specific IgE) were analyzed. The prevalence of AR symptoms was 9.1% (n=169), with no difference observed in either sex. The most commonly reported symptom was rhinorrhea (69.2%), followed by sneezing (32%) and nasal obstruction (20.7%). Symptoms were considered detrimental to the children's daily activities in 30 cases (17.8%). The authors suggested that universally accepted criteria to describe AR in infants are lacking. The study does not define diagnostic criteria for AR in infants; it investigates the association between AR symptoms, parental predisposition, and biological markers for atopy.

Chong et al.[12] reported that AR in young children is difficult to diagnose, and the symptoms are often confused with those of infectious rhinitis. However, symptoms that last longer than 2 weeks should prompt a search for causes other than infection. Chong et al.[12] studied 493 infants selected from a group of 1543 patients with asthma to assess the frequency of AR in infants with wheezing. Infants with 2 or more nasal symptoms (sneezing, itching, congestion, and rhinorrhea) were considered to have rhinitis. They highlighted that 367 (74%) infants with asthma were diagnosed with rhinitis, and 131 (36%) had sensitization to aeroallergens detected by a skin prick test and were diagnosed with AR. The study showed that rhinitis is commonly present in infants with wheezing. The authors concluded that the diagnosis and definition of AR remains challenging in young children.

Chong et al.[6] verified the prevalence, clinical features, and treatment of AR symptoms in the first year of life using the International Study of Wheezing in Infancy (EISL) Phase III questionnaire with the addition of modified questions about AR from the International Study of Asthma and Allergies in Childhood (ISAAC). The following questions were directed at caregivers of 1003 children: (1) Has your baby ever had problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?; (2) Has your baby used antihistamines when he/she had problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?; (3)

Table 1
Characteristics of the studies

Author/year	Country	Age	Sample size	Characteristics of the study	Diagnostic criteria	Definition of allergic rhinitis	Results
Herr M., et al., 2011	France	19 (SD, 2) months	1850	Cohort of children included in the PARIS birth control to describe the prevalence of symptoms suggestive of AR and to investigate the relationships between AR symptoms and atopy-related factors.	– Standard questionnaire directed at caregivers. – Blood eosinophils by flow cytometry. – Total serum immunoglobulin E (IgE). – Specific IgE for food and aeroallergens.	It does not define any criteria to diagnose AR in infants.	It reported an association between AR symptoms and biological markers of atopy (serum eosinophils and house dust mite sensitization). It suggested that AR may begin as early as 18 months.
Chong Neto H. J., et al., 2010	Brazil	0-24 months	493	Cross-sectional study to assess the frequency of rhinitis in infants with asthma.	– Standard questionnaire directed at caregivers. – Skin prick test with aeroallergens.	Rhinitis symptoms associated with sensitization to at least 1 aeroallergen through skin prick test.	367 infants (74%) were diagnosed with rhinitis and 131 (36%) with AR. Incidence of rhinitis in infants with asthma as well as atopic sensitization was similar to older children.
Chong Neto H. J., et al., 2014	Brazil	12-15 months	1003	Cross-sectional study to determine the prevalence, clinical characteristics, and treatment of AR symptoms in the first year of life.	– Standard questionnaire directed at caregivers: Phase III EISL questionnaire with the addition of modified questions from the ISAAC questionnaire.	It does not define any criteria to diagnose AR in infants.	In their first year of life, 484 infants (48.3%) had at least 1 symptom of rhinitis, in the absence of a cold or the flu. High prevalence of early AR symptoms.
Otsuka H., et al., 2018	Japan	2-120 months	302	Cross-sectional study to diagnose AR in infants using a unique protocol.	– Clinical questionnaire directed at caregivers. – Analysis of nasal cavity cells (neutrophils, eosinophils, and mast cells). – Serum IgE specific for food and aeroallergen.	Rhinitis symptom associated with eosinophils and/or mast cells on nasal swab and positive serum IgE for food and/or aeroallergen.	141 children < 2 years of age were diagnosed with AR. The association between sensitization to aeroallergens and AR in the age group under study is rare. Rhinitis symptoms and sensitization to food allergens may be associated in infants.
Osawa Y., et al., 2011	Japan	0-24 months	594	Cross-sectional study to evaluate the diagnosis of AR in infants.	– Clinical questionnaire directed at caregivers. – Serum IgE for aeroallergen. – Nasal eosinophils. – Nasal changes assessed by anterior rhinoscopy.	Aeroallergen sensitization associated with nasal eosinophils and intranasal examination with rhinorrhea and inferior turbinate hypertrophy.	The minimum prevalence of AR in children aged 18 months is estimated to be 1.5%. Diagnosis of AR in children < 2 years of age either by medical professionals or based on parent questionnaires is inaccurate.

AR = allergic rhinitis.

Has your baby used intranasal steroids when he/she had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?; and (4) Has your baby been diagnosed with AR by a doctor?. The study identified 484 babies (48.3%) who had at least 1 AR symptom in the first year of life and did not have an infection.

Otsuka et al.[4] stated that the onset of AR in infants is difficult to identify because it is challenging to make a conclusive diagnosis in young children. The authors conducted a study with 302 children (aged 2 to 120 months) to diagnose AR by combining different nasal cells and IgE for food and aeroallergens. Children with purulent rhinorrhea, common cold, systemic infectious disease, or eosinophilic syndrome were excluded. The study showed that 80% of children aged 2 to 14 months and 77% aged 15 to 24 months had rhinorrhea and only neutrophils on nasal swab, and the probable diagnosis was infectious rhinitis. No infants under 15 months of age had AR symptoms or specific IgE for an aeroallergen. However, AR symptoms were present in infants with sensitization to food allergens. The transition from food IgE response to aeroallergens occurred in infants older than 15 months, and sensitization to aeroallergens increased markedly after 25 months.

Osawa et al.[5] included 594 children (408 healthy infants and 186 who received medical care for various reasons) to determine the prevalence of sensitization to aeroallergens and the presence of nasal eosinophils in infants. In the group of healthy infants, 44 (10.7%) had allergen-specific IgE, 29 (7.1%) had nasal eosinophils, 8 (2%) had both, and 125 (30%) had rhinorrhea confirmed upon examination of the nasal cavity. Among the children who had sensitization to an aeroallergen in addition to nasal eosinophils, 6 (1.5%) had rhinorrhea confirmed upon physical examination. These children were diagnosed with AR. Among the 186 children who had attended the clinic, 5 (2.6%) had allergen-specific IgE and 6 (3.2%) had nasal eosinophils. No children had aeroallergen sensitization or nasal eosinophils. According to a questionnaire completed by the caregivers, 11 (2.7%) children had the diagnosis of AR made by a medical practitioner. However, sensitization to aeroallergen was confirmed in only 1 child, and none had nasal eosinophils. Thus, the authors stated that the diagnosis of AR based on parent questionnaires is unreliable. The authors concluded that diagnostic criteria for AR in children under 2 years of age need further definition to aid in early diagnosis and intervention.

Discussion

In clinical practice, accurate etiologic diagnosis of rhinitis in infants is challenging, and only few studies have evaluated the natural history of AR in the pediatric population.[8] Most recommendations are extrapolated from studies of adults and/or older children.

We could observe from the studies included in the present review that the definition of AR is not homogeneous. Herr et al.[11] and Chong et al.[6] used the term AR symptoms but have not defined the diagnosis of AR. In a previous study conducted in 2010, Chong et al.[12] defined AR as the presence of rhinitis symptoms associated with the sensitization to at least one aeroallergen. Otsuka et al.[4] and Osawa et al.[5] highlight the importance of the analysis of nasal swabs in addition to clinical symptoms and allergic sensitization.

The ISAAC defines rhinitis based on a positive response from children's caregivers to the question, "In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu?". The questionnaire does not include a comprehensive medical history and allergic sensitization testing, which results in low accuracy for the diagnosis of AR. A Korean study reported an estimated accuracy of 60% for the ISAAC questionnaire and considered that it overestimates the true prevalence of AR.[13] Osawa et al.[5] doubt the accuracy of studies based on questionnaires directed at children's caregivers, because in their study none of the children whose parents reported that they had been medically diagnosed with AR were actually diagnosed when the diagnostic criteria for AR were used by the authors.

The guidelines of the Allergic Rhinitis and its Impact on Asthma (ARIA)[14] and the Brazilian consensus[1] consider a comprehensive medical history (clinical history, rhinitis symptoms, personal and family history of atopy) combined with a careful physical examination and proof of allergic sensitization crucial for the diagnosis of AR. The diagnosis of AR is therefore clinical and associated with identification of the possible causative allergen through skin prick test for immediate hypersensitivity or specific IgE.[1,3,8,9]

According to the Japanese consensus on AR, a definite diagnosis is based on symptoms (sneezing, itching, watery rhinorrhea, and nasal obstruction) combined with a positive nasal eosinophil test and identification of causative allergens (skin prick test for immediate hypersensitivity or allergen-specific

serum IgE).[10] Thus, Otsuka et al.[4] and Osawa et al.[5] agree with the definition established by the Japanese scientific community.

The European Forum for Research and Education in Allergy and Airways diseases[2] has developed a consensus guideline for AR in the pediatric population. According to the document, the diagnosis of AR in children is based on a detailed clinical history, physical examination and, if necessary, testing for allergen-specific IgE.[2]

AR symptoms may be persistent or intermittent, usually occurring within minutes of exposure to the allergen. In young children, AR symptoms may manifest less clearly and may be more subjective, as they depend on the caregiver's perception. In addition, young children are more likely to have infectious rhinitis, which adds to the challenge of diagnosing AR.[2,8,9]

The hypothesis of AR becomes more likely when the following conditions are present: ocular involvement, noticeable itching (allergic salute), symptoms exacerbated by a potential allergen, and family and/or personal history of atopy.[2] A specialist should also consider the following signs: children with unilateral symptoms refractory to treatment, such as severe nasal obstruction and sleep apnea; children with nasal polyps; children under 2 years of age; and children with nasal symptoms since birth.[2]

Examination of the nasal cavity with anterior rhinoscopy is key for the diagnosis of AR and should always be performed.[8] Classically, nasal examination shows hypertrophic, pale lower or middle turbinates with clear secretion.[9] Osawa et al.[5] highlight the importance of examining the nasal cavity and report that, in their study, the presence of rhinorrhea and hypertrophic turbinates allowed the identification of more children with AR than when infants were assessed based only on parent-reported symptoms.

Allergen-specific IgE detection can be performed in any age group by skin prick test for immediate hypersensitivity or allergen-specific serum IgE.[2,15] In a meta-analysis, the sensitivity of the skin prick test ranged from 68% to 100% and the specificity from 70% to 91%. However, studies of young children were not included.[16]

The poor agreement between skin prick test for immediate hypersensitivity and allergen-specific serum IgE and the poor correlation with clinical symptoms in young children suggest that allergy testing should be performed only in children with symptoms of atopic disease, rather than as a diagnostic screening method.[15] Therefore, allergic sensitization test results should be interpreted in light of the clinical history, as both false-positive and false-negative results can occur.[2]

Conclusion

Few studies have investigated diagnostic criteria for AR in infants, and consensus guidelines provide recommendations based on data extrapolated from older populations.

The variability and nonspecific nature of AR clinical symptoms in infants, combined with the fact that sensitization to aeroallergens does not necessarily have clinical significance, represent a challenge for the correct diagnosis of AR in young children. Thus, it is critical that the attending physician performs a careful history-taking and physical examination, including the nasal cavity, as well as tests to detect allergic sensitization (skin prick test for immediate hypersensitivity and/or allergen-specific serum IgE), whose results should be correctly interpreted and correlated with the patient's clinical history and physical examination. Differential diagnoses should also be considered.

AR in childhood has an impact on the quality of life of patients and their family members. In addition, it is a strong predictor of asthma in adolescents and adults.[1,2] Therefore, it is clear that accurate diagnosis and effective treatment of AR in childhood are highly important, with benefits that include not only improvement of patients' quality of life but also prevention of new atopic sensitizations.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Associations between house dust mites and prevalence of asthma and allergic rhinitis among school-age adolescents in the south of Brazil

Associações entre ácaros da poeira domiciliar e prevalência de asma e rinite alérgica em adolescentes em idade escolar no sul do Brasil

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ABSTRACT

Background: Allergic reactions resulting from exposure to environmental allergens are responsible for problems such as asthma and allergic rhinitis. House dust mites (HDMs) are one of the most important causes of allergic sensitization and a major source of allergens worldwide. **Objective:** To investigate associations between the presence of HDMs in the homes of adolescents aged 13 to 14 years and the prevalence of respiratory problems using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. **Methods:** A total of 103 adolescents from the city of Lajeado, south of Brazil, participated in the ISAAC Protocol, and 10 homes were sampled for dust collection. **Results:** Regarding the medical history of asthma and rhinitis, a prevalence of 14.7% of asthma was found, and 68.9% of the adolescents have already had rhinitis. The investigation of active asthma and rhinitis showed that 5.15% of adolescents had symptoms of asthma and 39.14% had symptoms of allergic rhinitis. Premature birth, low birth weight and smoking mother were shown to be risk factors for the development of asthma and allergic rhinitis. HDMs were mostly found on the carpet (46.80%), followed by bed (34.04%) and sofa (14.89%); curtains had the fewest mites (4.25%). *Dermatophagoides pteronyssinus* (46.0%) and *Dermatophagoides farinae* (31.91%) were the most frequently found species. **Conclusion:** The homes of adolescents with respiratory problems had a large number of HDMs.

Keywords: Allergy and Immunology, asthma, mites, dust, allergic rhinitis.

RESUMO

Introdução: As reações alérgicas resultantes da exposição a alérgenos ambientais são responsáveis por problemas como asma e rinite alérgica. Os ácaros conhecidos como ácaros da poeira domiciliar (HDMs) são uma das causas mais importantes de sensibilização alérgica e representam uma das fontes de alérgenos mais importantes do mundo. **Objetivo:** O presente estudo tenta encontrar uma relação entre a presença de HDMs nas residências de adolescentes de 13 a 14 anos e a prevalência de problemas respiratórios, usando o questionário ISAAC (*International Study of Asthma and Allergies in Childhood*). **Método:** Participaram do Protocolo ISAAC 103 adolescentes da cidade de Lajeado (RS), dez domicílios foram amostrados para coleta de poeira. **Resultados:** Em relação à história clínica de asma e rinite, foi encontrada prevalência de 14,7% de asma, sendo que 68,9% dos adolescentes já apresentaram rinite. A investigação de asma e rinite ativa mostrou que 5,15% dos adolescentes apresentaram sintomas de asma e 39,14% apresentaram sintomas de rinite alérgica. Nascimento prematuro, baixo peso ao nascer e mãe fumante demonstraram ser fatores de risco para o desenvolvimento de asma e rinite alérgica. O local onde foi encontrado o maior número de ácaros foi tapete (46,80%), seguido de cama (34,04%), sofá (14,89%); cortina foi o local com menor número de ácaros encontrados (4,25%). *Dermatophagoides pteronyssinus* (46,0%) e *Dermatophagoides farinae* (31,91%) foram as espécies mais encontradas na poeira. **Conclusão:** As residências de adolescentes com problemas respiratórios apresentaram um maior número de HDMs.

Descritores: Alergia e Imunologia, asma, ácaros, poeira, rinite alérgica.

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Introduction

Allergic reactions triggered by exposure to environmental allergens are responsible for the occurrence of problems such as asthma and allergic rhinitis.[1] The diseases caused by these reactions depend on genetic and environmental factors, and represent an important public health issue,[2] since they are a frequent cause of morbidity in the pediatric population.[3]

Allergic rhinitis is one of the most prevalent chronic diseases worldwide, with high impact on the quality of life of patients in different age groups.[4] Furthermore, its prevalence has increased over the years and is likely to be underestimated, since many individuals do not consider it a disease and thus do not seek medical help.[5] Even so, allergic rhinitis ranks among the 10 most frequent causes of demand for primary health care. Its major symptoms are nasal obstruction/pruritus, aqueous rhinorrhea, sneezing, and ocular symptoms.[6]

Asthma is characterized by several symptoms, such as wheezing, dyspnea, chest pain, and/or coughing, and by reduced expiratory airflow. These symptoms, as well as limited airflow, are characteristics that vary according to intensity and time elapsed. These variations are frequently triggered by factors such as exercising, exposure to irritating factors or allergens, changes in weather, or viral infections. According to the international recommendations of the Global Initiative for Asthma, asthma is a common chronic respiratory disease that affects approximately up to 20% of the global population.[7] Therefore, asthma and allergic rhinitis have close interrelations of pathophysiological, epidemiological, morphological, and clinical nature, and that is why they started to be considered as manifestations of the same pathological process: contiguous allergic inflammation of the airways.[8] In 2014 and 2015, a total of 126,626 hospitalizations for asthma were reported in Brazil, 63% of which occurred in children below 14 years old.[9] The largest incidence was in the northeastern region, with 55,876 cases; of those, 16,181 cases involved 1- to 4-year-old children. Ceará stands out in this scenario, with 6,432 cases.[10]

Due to the impact of allergic rhinitis and asthma on people's lives, the International Study of Asthma and Allergies in Childhood (ISAAC) can be considered an effective study method for the epidemiological diagnosis of these allergic diseases.[11] The ISAAC performed in Brazil showed that the mean prevalence of symptoms related to allergic rhinitis was 29.6% among adolescents and 25.7% among school-age adolescents. Regarding symptoms related to active asthma, mean prevalence was 19.0 and 24.3% among adolescents and school-age adolescents, respectively. Brazil is in the group of countries that have the highest prevalence rates for asthma and allergic rhinitis worldwide.[12]

Mites are the most important cause of allergic sensitization, and differences have been observed both in their geographical distribution and in the sensitization profile.[1] House dust mites represent one of the most important sources of allergens worldwide. The mites *Dermatophagoides pteronyssinus* (Trouessart, 1897) and *Blomia tropicalis* (Bronswijck, Cock & Oshima, 1973) are the primary sensitizers of patients diagnosed with asthma and allergic rhinitis.[13]

The aim of the present study was to analyze the relationship between the presence of house dust mites in the homes of 13- and 14-year-old adolescents and the prevalence of allergic rhinitis and asthma, by using the ISAAC Protocol and collecting house dust. A larger amount of mites was expected to be found in the homes of adolescents that suffer from asthma or allergic rhinitis. Additionally, the percentage of these diseases found in the target population investigated in the city of Lajeado was expected to be similar to that of other cities in Brazil.

Material and methods

Study population and area

The present study was conducted in August, September, and November 2020, with 13- and 14-year-old adolescents from a public school in the city of Lajeado, state of Rio Grande do Sul (RS), Brazil. Lajeado is located in the Taquari River Valley, central region of the state of Rio Grande do Sul. This valley is comprised of 36 municipalities that cover an area of approximately 4,826.7 km^2 (1.71% of the state), according to data by the Statistics and Economy Foundation (Fundação de Economia e Estatística, FEE).[14]

ISAAC Protocol

In order to investigate respiratory diseases, the written and supplementary questionnaires of the ISAAC Protocol were used and applied, with objective questions designed to check the presence

of respiratory diseases such as asthma, rhinitis, and eczema. Parents also answered questions regarding the characteristics of the homes where the adolescents lived, as well as diet and immunization, in order to keep track of factors that might be related to respiratory diseases. All parents agreed and signed an Informed Consent Form. Because the study was conducted during the pandemic period caused by SARS-CoV-2, the ISAAC questionnaire was set up on the Google Forms platform and was available for the adolescents' parents. In the ISAAC protocol, there are questions related to birth weight, breastfeeding period, immunization, characteristics of the house, and that is why the protocol was applied to the adolescents' parents, in order to have more accurate answers. During the research period, the school had 146 students aged between 13 and 14 years old, all of them received the link to access the questionnaire, but we had a return of 107 parents, with 73.28% of parents joining the study. However, of the 107 forms returned, four were disregarded, since they were incorrectly completed; thus, 103 questionnaires were validated in the study.

House dust mite sampling

After applying the ISAAC questionnaire, the homes of five adolescents with respiratory problems and five adolescents with no respiratory problems were randomly selected for house dust collection. Only five homes from each group were evaluated, because the study was conducted during the pandemic period caused by SARS-CoV-2. However, this sample represents more than 10% of the population of adolescents with and without respiratory problems. Dust samples were vacuumed from the following sites: sofa, mattress, carpet, and curtain. This sampling was performed using a portable Black & Decker Dust Buster 750W and 220V vacuum cleaner. Samplings were conducted for 9 minutes; on average, 3 minutes at the sofa and 2 minutes at the other sites. After sampling each site, the dust was removed from the vacuum cleaner using a medium-tipped brush (n. 16), individually kept in plastic pots, and stored under refrigeration at 7°C until the samples were screened.[15]

Screening of house dust and species identification

Dust was screened using a Leica - S6E-LED 2500 stereoscopic microscope, and the mites found were removed using a thin-tipped brush and mounted onto slides in Hoyer's medium.[16] Mounted slides were maintained in a drying furnace for a period of 10 days, for clarification of specimens and medium drying. Specimens were identified using a Zeiss Imager.Z2 phase-contrast optical microscope and dichotomous keys provided by Hughes, Flechtmann, and Krantz & Walter.

Data analysis

The questionnaire answers were analyzed using SPSS 10, performing a multiple regression analysis. Descriptive statistics was performed treating the adolescents who were part of the study as parameters, and the data obtained were presented as percentages.

Ethical aspects

This study was approved by the Research Ethics Committee of Universidade do Vale do Taquari - Univates (CAAE: 28747220.4.0000.5310).

Results

ISAAC Protocol

Regarding the clinical history of asthma and rhinitis, 14.7% have already had asthma, and 68.9% have already had rhinitis. In the investigation of active asthma and rhinitis, 5.15% of the adolescents had at least one to three wheezing episodes in the previous 12 months, interference of wheezing with sleep in the previous year, and nocturnal cough, which characterized the presence of symptoms of asthma. Regarding rhinitis, 39.14% of the adolescents has had the following problems in the previous 12 months: sneezing, running nose, or blocked nose without having the flu or a cold, and this problem was also followed by lacrimation or itchy eyes, thus characterizing active rhinitis.

The asthma-rhinitis association rate in the population of adolescents of the present study was 3.09% (Figure 1). The highest rhinitis prevalence was observed in June, accounting for 44.4% of the cases. The month with the lowest prevalence was November, with 7.4% (Figure 2).

The prevalence of asthma or allergic rhinitis was observed to decrease proportionally with increased birth weight: 100% for adolescents with birth weight

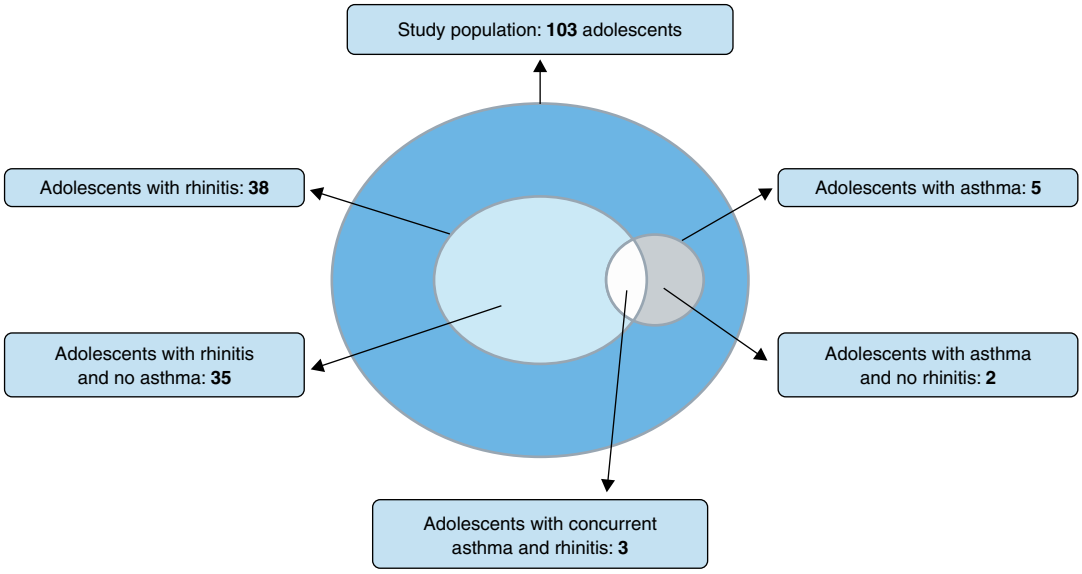

Figure 1
Asthma-rhinitis association rate in 13- to 14-year-old adolescents

between 1,500 and 1,999 g had either asthma or allergic rhinitis; from 2,000 to 2,499 g, the prevalence found was 40%; and from 2,500 to 3,499 g, the prevalence was 39.68%. Additionally, in adolescents who were born with over 3,500 g, the prevalence of either asthma or allergic rhinitis dropped to 34.48%.

Regarding the birth of adolescents, 50% of those who were born prematurely, either through normal delivery or C-section, had respiratory problems in the present study. Among the group of adolescents who were not born prematurely, those who were born through C-section had a prevalence of 34.42% of these problems, and those who were delivered through normal labor had a prevalence of 42.42%.

The prevalence of asthma and allergic rhinitis in adolescents whose mothers were former or current smokers was 54.54%. On the other hand, the prevalence was 32.98% in the group of adolescents whose mothers were non-smokers. In homes of adolescents with visible mold stains on the walls or ceiling, the prevalence of respiratory problems investigated in the present study was 50%, while the prevalence in the other homes was 31.08%.

House dust mites

The initial study hypothesis was corroborated by the findings in the present study: there was a higher number of mites in the homes of adolescents who had asthma or allergic rhinitis. A total of 47 dust mites were found, collected from the homes of 13- and 14-year-old adolescents (Table 1). Of this total, 74.47% were found in homes of adolescents with respiratory problems, and 25.53% were found in homes of adolescents with no respiratory problems.

No mites were found in two of the 10 homes where house dust was sampled, and these two homes belonged to adolescents with no respiratory problems.

The site with the highest number of mites was the carpet (46.80%), followed by bed (34.04%) and sofa (14.89%); curtains were the site with the lowest number of mites (4.25%). The six species identified in the present study belong to three families: *Pyroglyphidae*, *Glycyphagidae*, and *Cheyletidae*. *Dermatophagoides pteronyssinus* (46.80%) and *D. farinae* (31.91%) accounted for 78.71% of the total individuals found.

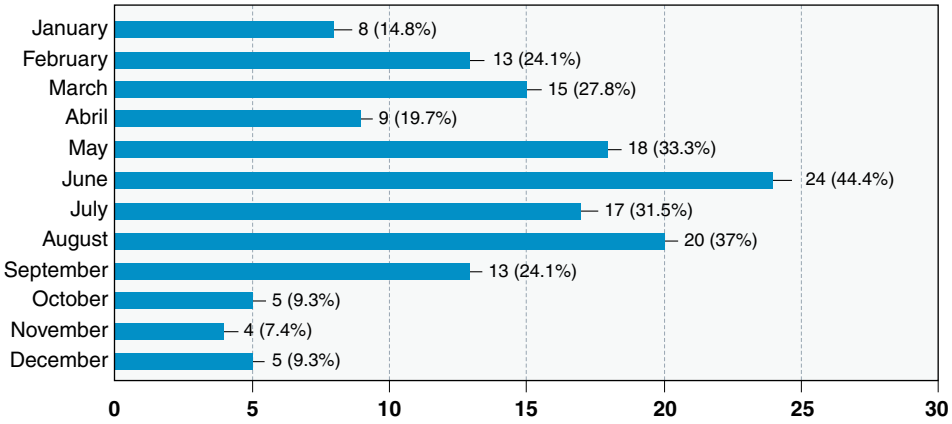

Figure 2
Prevalence of allergic rhinitis throughout the year

Table 1
House dust mite families and species found in the homes of 13- and 14-year-old adolescents in the south of Brazil

Family/species	Sofa	Bed	Rug	Curtain	Total
Pyroglyphidae					
Dermatophagoides pteronyssinus	6	5	9	2	22
Dermatophagoides farinae	1	7	7	–	15
Euroglyphus sp.	–	1	2	–	3
Glycyphagidae					
Blomia tropicalis	–	–	1	–	1
Glycyphagus destructor	–	2	–	–	2
Cheyletidae					
Cheyletus malaccensis	–	1	3	–	4
Total	7	16	22	2	47

Discussion

The initial study hypothesis was corroborated by the findings: the percentages of allergic rhinitis and asthma found in the target population investigated in the city of Lajeado were similar to those found in other cities in Brazil. In a study conducted by Toledo[17] in São Paulo with 13- and 14-year-old adolescents, also applying the ISAAC Protocol, the prevalence of asthma and rhinitis were similar to those of the present study. Prevalence values of asthma and rhinitis were 6.8% and 37.6%, respectively.

At phase three of the ISAAC, the following prevalence values of active asthma were found in 13- and 14-year-old adolescents in the following cities of Rio Grande do Sul: Passo Fundo (20.5%), Porto Alegre (18.2%), and Santa Maria (15.3%).18 Fernandes et al.,[19] in a study conducted in the city of Pelotas, observed prevalence values of asthma and allergic rhinitis symptoms of 19.8% and 35.3%, respectively.

Silva et. al.,[20] who investigated the prevalence of asthma and rhinoconjunctivitis in 13- and 14-year-old adolescents in Florianópolis, state of Santa Catarina, Brazil, observed an association between these two diseases in 4.5% of the adolescents. Percentage that is close to the association found in our study (3.09%).

A study conducted by Esteves et al.[21] also showed that May, June, July, and August were the months when symptoms of rhinitis worsened, which might be explained by the fact that this is a colder period, with lower humidity, thus increasing the concentration of aeroallergens. A study on house dust conducted by Nascimento et al.[15] found a lower number of mites in the summer compared to winter, autumn, and spring months, thus showing that colder months and higher presence of mites, in fact, are related to the worsening of rhinitis symptoms.

In our study, adolescents with a lower birth weight had a higher prevalence of respiratory problems, and this corroborates the study conducted by Fernandes et. al.,[22] who showed that symptoms of asthma were associated with birth weight less than 2,500 g. A study conducted by Neto et. al.[23] has already shown also that being born prematurely is a risk factor for asthma and allergic rhinitis.

Dermatological reactions after being in contact with mites of the family Cheyletidae have already been described by Yoshikawa[24] and Ezequiel et al.[25] However, their clinical importance has been poorly acknowledged due to the lack of available commercial extracts to perform skin-prick tests. Additionally, *Cheyletus malaccensis*, found in the house dust collected, has already been reported as a predator of *Dermatophagoides farinae*, which indicates its association with dust mites, as a potential predator to be used in the biological control of dust mites and stored product mites.[26] A study conducted by Dutra et al.[27] in Porto Alegre, state of Rio Grande do Sul, Brazil, evaluating mite fauna in house ecosystems, found that *D. pteronyssinus* was the most frequently found species too, with prevalence value of 39.6%.

A cross-sectional study conducted by Li et al.[28] with 6,304 patients who had asthma and/or rhinitis showed that the severity of rhinitis and asthma was significantly correlated to the skin index of sensitization against the mites *D. pteronyssinus*, *D. farinae* and *Blomia tropicalis* by performing hyperresponsiveness tests. This reinforces the findings regarding the association of a higher presence of mites in homes of adolescents with respiratory problems.

Conclusions

In conclusion, the prevalence of allergic rhinitis in the age group studied, in the city of Lajeado, is similar to that of other regions in the state of Rio Grande do Sul and Brazil. The prevalence of asthma, on the other hand, was lower compared to that of these locations. Premature birth, low birth weight, and smoking mother were shown to be risk factors for the development of asthma and allergic rhinitis. Homes of adolescents with respiratory problems had a higher number of house dust mites, which can be explained by the fact that these adolescents are more prone to having asthma and allergic rhinitis.

The results found can be used as information for the development and implementation of strategies for preventing sensitization against house dust mites. They are also important for conducting practices related to allergic diseases associated with these mites.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Quality of life assessment in pediatric patients with food allergy

Análise da qualidade de vida em pacientes pediátricos com alergia alimentar

Analice Val de Paula[1], Lídia Lacerda Guimarães[1], Leticia Luisa Mattos[2], Luiza Elian Reis[2], Érica Godinho Menezes[2], Wilson Rocha Filho[1]

ABSTRACT

Background: Food allergy can affect the well-being of patients and their families. **Objective:** To investigate the quality of life of patients with food allergy followed up at a multidisciplinary treatment center using a validated questionnaire. **Methods:** Patients aged 0 to 18 years followed up at the Food Allergy Outpatient Clinic of João Paulo II Pediatric Hospital between 2012 and 2017 were invited to answer a quality-of-life assessment questionnaire for information on type of allergy, clinical presentation, presence of atopic dermatitis, prescription of an epinephrine kit, duration of follow-up at the clinic, and duration of follow-up with a dietitian. **Results:** A total of 77 patients were included, with a mean age of 3.38 years. Most participants rated their quality of life as fair (43%) and had less than 6 months of outpatient follow-up (52%). From those meeting with a dietitian, 52.4% had less than 6 months of follow-up. Immunoglobulin E (IgE)-mediated allergy was identified in 51% of participants, and 66.66% of them required an epinephrine kit. There was no statistically significant association between quality of life and the study variables. **Conclusion:** A quality-of-life assessment questionnaire is an important tool for evaluating patients with food allergy, allowing us to profile these patients and to act individually on issues that might negatively impact their daily lives.

Keywords: Child, food hypersensitivity, quality of life, child health.

RESUMO

Introdução: A alergia alimentar pode afetar o bem-estar dos pacientes e de seus familiares. Esse trabalho busca, por meio de questionário validado, investigar a qualidade de vida desses pacientes, acompanhados em um centro de tratamento multidisciplinar. **Métodos:** Pacientes entre 0 e 18 anos, monitorados no Ambulatório de Alergia Alimentar do Hospital Infantil João Paulo II entre 2012 e 2017, foram selecionados para responder a um questionário de avaliação de qualidade de vida com coleta de informações acerca do tipo de alergia, sua apresentação clínica, presença de dermatite atópica, prescrição ou não de *kit* de Adrenalina®, tempo de acompanhamento no serviço e tempo de acompanhamento por nutricionista. **Resultados:** Foram incluídos 77 pacientes, com idade média de 3,38 anos, em sua maioria revelando qualidade de vida regular (43%) e com acompanhamento no Serviço inferior a seis meses (52%). Daqueles acompanhados por nutricionista, 52,4% o faziam há menos de seis meses. Alergia IgE mediada foi identificada em 51% dos sujeitos da pesquisa, com 66,66% dos mesmos sob prescrição de *kit* de Adrenalina®. Não houve associação estatisticamente significativa entre qualidade de vida e as variáveis analisadas. **Conclusão:** O questionário de qualidade de vida é um importante instrumento de avaliação de pacientes com alergia alimentar, permitindo traçar o perfil dos mesmos e atuar individualmente nos quesitos que impactam negativamente o seu dia a dia.

Descritores: Criança, hipersensibilidade alimentar, qualidade de vida, saúde da criança.

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Introduction

Food allergy, an abnormal immune response to food proteins, may be immunoglobulin (IgE)-mediated, partially IgE-mediated, or non-IgE-mediated.[1,2] It affects more children than adults and its prevalence has been increasing worldwide in recent years, estimated at approximately 6% in children < 3 years of age and 3.5% in adults.[3] Patients with this condition are at risk of developing serious reactions that, if not treated properly, can be fatal.

Restricting the intake of allergenic food proteins is essential for treatment, which requires discipline on the part of the patient and the patient's family. For example, labels on manufactured products must be carefully read in light of the possibility of cross-contamination, and some school and social activities involving food intake must be restricted.[4] Furthermore, children with anaphylaxis should carry adrenaline kits, and their guardians should receive adequate training in their use. Thus, diagnosis of a food allergy can compromise the quality of life of patients and their families, and psychiatric disorders can result.[5-7] Such outcomes are especially prevalent in school-age children.[8]

Many quality of life questionnaires have been developed for children and adolescents with food allergies, seeking a better understanding of the impact of diagnosis and treatment in the daily lives of patients and their families.[9-12] In this context the present study was developed, aiming to investigate the quality of life of patients assisted at a reference center for multidisciplinary treatment of food allergies by applying a validated questionnaire.

Methods

Study design and population

This cross-sectional, descriptive study was conducted at the Food Allergy Clinic of the Hospital Infantil João Paulo II – Fundação Hospitalar do Estado de Minas Gerais between 2012 and 2017. This center offers care by a multidisciplinary team of doctors from different specialties (pediatricians, allergists, pediatric gastroenterologists, dermatologists), nurses, and nutritionists.

We included patients ≤ 18 years of age whose food allergy diagnosis was confirmed through clinical history, showing an irrefutable cause and effect relationship, in addition to reproducible symptoms from repeated exposure to the suspected food. When necessary, an immediate skin test was performed and specific IgE dosage for the food was determined, or an oral provocation test was performed. Patients with non-IgE-mediated food allergies were included when they had a reproducible and irrefutable clinical history with the food in question. When necessary, these patients were given an oral provocation test to confirm the diagnosis. Eosinophilic esophagitis was confirmed by macroscopic findings from an upper digestive endoscopy, complemented by histology showing ≥ 15 eosinophils per field. Data were collected from all patients (both personal and disease-related) using a specific form.

Patients with a history of anaphylaxis received an adrenaline kit and their parents/ caregivers were trained in its correct handling. Patients and/or family members/ caregivers who were unable to adequately fill out the questionnaires, as well as patients with congenital and/or systemic diseases that could compromise their quality of life, were excluded from the study.

Quality of Life Questionnaire

Standardized questionnaires for assessing quality of life in food allergy patients, originally developed in English by DunnGalvin et al.,[9] were applied to patients and their parents, caregivers or legal guardians, with the same person responding throughout the study. First, we validated Portuguese versions of the questionnaires at our service. During the translation and adaptation process, the questionnaires were filled out by the same caregiver on 2 occasions, with a maximum interval of 1 week between applications. Agreement > 90% was found between the applications. After this, the questionnaires were applied every 3 months. Questionnaires for patients ≤ 12 years of age were only filled out by parents/ caregivers, while those for patients 13-18 years of age were filled out partly by the patients and partly by their parents/caregivers.

In general terms, the questions addressed 3 domains involved in the disease: emotional impact, food anxiety, and social and dietary limitations. Each item presents options for quantifying the impairment of the patient's quality of life on a scale from 1 (none) to 6 (extreme). The final result is the mean of the sum of the mean values obtained in each domain. Values 0-2, 3-4, and 5-6 indicate good, average, and poor quality of life, respectively (Appendices 1, 2 and 3).

Statistical analysis

The data were analyzed using IBM SPSS Statistics 16.0. The following variables were considered: quality of life (poor, average, or good), follow-up time at our service, follow-up with a nutritionist (and duration), allergy type (IgE-mediated, non-IgE-mediated, or mixed), diagnosis according to the clinical presentation of the allergy, and adrenaline kit prescription. The statistical tests included chi-square, Student's *t*-test, and the Kruskal-Wallis test. $P < 0.05$ was considered statistically significant.

Results

Initially, 90 patients were selected, of whom 13 (14.4%) were excluded either due to clinical follow-up failure or incorrect questionnaire completion. Thus, the study was based on data from 77 patients, of whom 41 (53.2%) were male and 36 (46.8%) were female, with a mean age of 3.38 years (Figure 1).

Quality of life (Table 1) was analyzed in the context of the following variables: follow-up time at our service, follow-up with a nutritionist (and duration), classification and clinical presentation of allergy, and prescription or not of an adrenaline kit (Tables 2 and 3). Regarding patient follow-up time (Table 4), 22 (28.5%) were monitored for > 12 months, 15 (19.5%) for 6-12 months, and 40 (52%) < 6 months. Among the latter group, after diagnosis and follow-up, the quality of life was good, average, and poor in 19 (47.5%), 15 (37.5%), and 6 (15.0%) patients, respectively. Of the 15 patients followed from 6-12 months, quality of life was good, average, and poor in 6 (40.0%), 6 (40.0%), and 3 (20.0%), respectively. Finally, of the 22 patients followed up > 12 months, the quality of life was good, average, and poor in 6 (27.3%), 12 (54.5%), and 4 (18.2%), respectively. The association between quality of life and follow-up time was not significant ($p = 0.602$).

Of the total sample, 42 patients (54.5%) were followed up by a nutritionist for variable periods (Table 5): 22 for < 6 months (52.4%); 9 for 6-12 months (21.4%); 11 for > 12 months (26.2%). The quality of life of these patients was good, average, and poor in 19 (45.2%), 18 (42.9%), and 5 (11.9%), respectively. There was no significant association ($p = 0.382$) between quality of life and follow-up with a nutritionist, or between quality of life and follow-up time with a nutritionist (Table 6). Of the 22 patients followed up ≤ 6

Table 1
Quality of life in the study population

Classification	Frequency	
	n	%
Good	31	40.3
Average	33	42.8
Poor	13	16.9

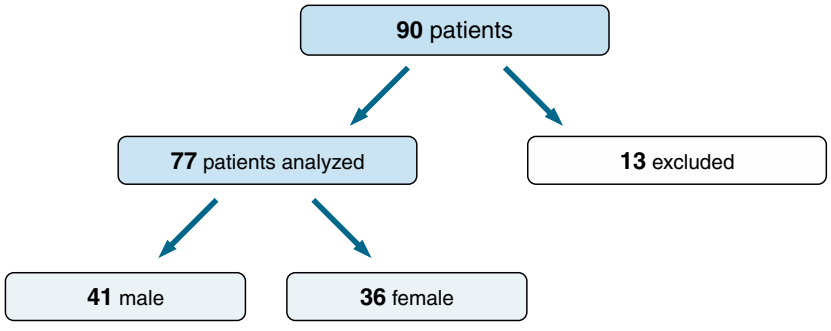

Figure 1
Patient selection flowchart

Table 2
Description of the population studied

Characteristics	n	%
Follow-up with nutritionist		
Yes	42	54.5
No	35	45.5
Adrenaline kit		
Yes	26	33.8
No	51	66.2
Atopic dermatitis		
Yes	31	40.8
No	45	59.2
No data	1	–
Follow-up time at service		
< 6 months	40	52
6-12 months	15	19.5
>12 months	22	28.5
Follow-up time with nutritionist		
< 6 months	22	52.4
6-12 months	9	21.4
>12 months	11	26.2
Not applicable	35	–
Allergy type		
IgE-mediated	39	50.6
Non-IgE-mediated	20	26.0
Mixed allergy	18	23.4
Clinical presentation of allergy		
Proctitis	12	15.6
FPIES	8	10.4
Eosinophilic esophagitis	3	3.9
IgE-mediated allergy	39	50.6
Atopic dermatitis as a single presentation	15	19.5

FPIES = Food Protein Induced Enterocolitis Syndrome.

Table 3
Comparison between follow-up with a nutritionist, adrenaline kit prescription, atopic dermatitis, follow-up time at the service, follow-up time with a nutritionist, allergy type, clinical presentation of the allergy, and quality of life (QOL) classification

Characteristics	Good QoL	Average QoL	Poor QoL	p-value
Follow-up with nutritionist				
Yes	19 (45.2%)	18 (42.9%)	5 (11.9%)	0.382
No	12 (34.3%)	15 (42.9%)	8 (22.8%)	
Adrenaline kit				
Yes	8 (30.8%)	13 (50%)	5 (19.2%)	0.503
No	23 (45.1%)	20 (39.2%)	8 (15.7%)	
Atopic dermatitis				
Yes	13 (41.9%)	13 (41.9%)	5 (16.2%)	0.934
No	17 (37.8%)	20 (44.4%)	8 (17.8%)	
Follow-up time at service				
< 6 months	19 (47.5%)	15 (37.5%)	6 (15%)	0.602
6-12 months	6 (40%)	6 (40%)	3 (20%)	
> 12 months	6 (27.3%)	12 (54.5%)	4 (18.2%)	
Follow-up time with nutritionist				
< 6 months	13 (59.1%)	8 (36.4%)	1 (4.5%)	0.257
6-12 months	3 (33.3%)	4 (44.5%)	2 (22.2%)	
>12 months	3 (27.2%)	6 (54.6%)	2 (18.2%)	
Allergy type				
IgE-mediated	12 (30.8%)	19 (48.7%)	8 (20.5%)	0.082
Non-IgE-mediated	11 (55%)	9 (45%)	0 (0)	
Mixed allergy	8 (44.4%)	5 (27.8%)	5 (27.8%)	
Clinical presentation				
Proctitis	7 (58.4%)	5 (41.6%)	0 (0)	0.232
FPIES	4 (50%)	4 (50%)	0 (0)	
Eosinophilic esophagitis	1 (25%)	0 (0)	2 (75%)	
IgE-mediated allergy	12 (30.8%)	19 (48.7%)	8 (20.5%)	
Atopic dermatitis	7 (46.6%)	5 (33.4%)	3 (20%)	

FPIES = Food Protein Induced Enterocolitis Syndrome.

Table 4
Relationship between follow-up period and quality of life (QoL)

	< 6 months	6-12 months	>12 months
Good QoL	19 (47.5%)	6 (40%)	6 (27.3%)
Average QoL	15 (37.5%)	6 (40%)	12 (54.5%)
Poor QoL	6 (15%)	3 (20%)	4 (18.2%)
Total	40 (52%)	15 (19.5%)	22 (28.5%)
P-value		0.602	

months, quality of life was good, average, and poor in 13 (59.1%), 8 (36.4%), and 1 (4.5%) respectively. In those followed up 6-12 months, quality of life was good, average, and poor in 3 (33.3%), 4 (44.5%), and 2 (22.2%), respectively. Finally, among those followed up > 12 months, quality of life was good, average, and poor in 3 (27.3), 6 (54.6%), and 2 (18.2%), respectively (Table 5).

IgE-mediated allergy was identified in 39 patients, among whom quality of life was good, average, and poor in 12 (30.8%), 19 (48.7%), and 8 (20.5%), respectively. Of the 20 patients with non-IgE-mediated allergy, quality of life was good and average in 11 (55.0%) and 9 (45.0%), respectively. Finally, among the 18 patients with mixed allergy, quality of life was good, average, and poor in 8 (44.4%), 5 (27.8%),

Table 5
Relationship between follow-up period with a nutritionist and quality of life (QoL)

	< 6 months	6-12 months	>12 months
Good QoL	13 (59.1%)	3 (33.3%)	3 (27.2%)
Average QoL	8 (36.4%)	4 (44.5%)	6 (54.6%)
Poor QoL	1 (4.5%)	2 (22.2%)	2 (18.2%)
Total	22 (52.4%)	9 (21.4%)	11 (26.2%)
Total		42 (54.5%)	
P-value		0.257	

and 5 (27.8%), respectively. The association between quality of life and allergy type was not significant (Table 7).

Regarding clinical presentation of the allergy, among the 12 patients with proctitis (15.6%), quality of life was good in 7 (58.4%) and average in 5. Of the 8 patients with food protein-induced enterocolitis syndrome (10.4%), quality of life was good in 4 (50%) and average in 4 (50%). Of the 3 patients with eosinophilic esophagitis (3.9%), quality of life was good in 1 (25%) and poor in 2 (75%). Of the 39 patients with IgE-mediated allergy (50.6%), quality of life was good, average, and poor in 12 (30.8%), 19 (48.7%), and 8 (20.5%), respectively. Of the 31 patients with atopic dermatitis (40.2%), quality of life was good, average, and poor in 13 (41.9%), 13 (41.9%), and 5 (16.2%), respectively. Of the 15 patients in whom atopic dermatitis was the only manifestation (19.5%), quality of life was good, average, and poor in 7 (46.68%), 5 (33.4%), and 3 (20%), respectively. There was also no significant association between quality of life and clinical presentation of food allergy (Table 8).

Adrenaline kits were prescribed to 26 (66.66%) of 39 patients with IgE-mediated allergy. Of these, quality

Table 6
Relationship between follow-up with a nutritionist and quality of life (QoL)

	Follow-up with a nutritionist	No follow-up with a nutritionist
Good QoL	19 (45.2%)	12 (34.3%)
Average QoL	18 (42.9%)	15 (42.9%)
Poor QoL	5 (11.9%)	8 (22.8%)
Total	22 (52.4%)	9 (21.4%)
P-value	0.382	

Table 7
Relationship between food allergy pathophysiology and quality of life (QoL)

	IgE-mediated allergy	Non-IgE-mediated allergy	Mixed allergy
Good QoL	12 (30.8%)	11 (55.0%)	8 (44.4%)
Average QoL	19 (48.7%)	9 (45.0%)	5 (27.8%)
Poor QoL	8 (20.5%)	2 (22.2%)	5 (27.8%)
Total	39 (50.6 %)	20 (26.0%)	18 (23.4%)
P-value	0.082		

Table 8
Relationship between diagnosis of food allergy and quality of life (QoL)

	Proctitis	FPIES	Eosinophilic esophagitis	IgE-mediated allergy	Atopic dermatitis	Atopic dermatitis as only manifestation
Good QoL	7 (58.4%)	4 (50%)	1 (25%)	12 (30.8%)	13 (41.9%)	7 (46.68%)
Average QoL	5 (41.6%)	4 (50%)	0	19 (48.7%)	13 (41.9%)	5 (33.4%)
Poor QoL	0	0	2 (75%)	8 (20.5%)	5 (16.2%)	3 (20%)
Total	12 (15.6%)	8 (10.4%)	3 (3.9%)	39 (50.6%)	31 (40.2%)	15 (19.5%)
P-value			0,232			

FPIES = Food Protein Induced Enterocolitis Syndrome.

of life was good, average, and poor in 8 (30.8%), 13 (50%), and 5 (19.2%), respectively. Once again, the association between these variables was not significant (Table 9).

Most of the patients followed up < 6 months had good quality of life. Most of the patients followed up > 12 months had average quality of life. Of the total number of patients, approximately 50% were followed up with a nutritionist (generally for < 6 months), and had good quality of life.

When analyzing patients according to food allergy type, approximately 50% had an IgE-mediated allergy and average quality of life. However, those with non-IgE-mediated or mixed allergies generally had good quality of life. IgE-mediated allergy and atopic dermatitis were the main clinical presentations, with

Table 9
Relationship between prescribing adrenaline kits for patients with IgE-mediated allergies and quality of life

	Received an adrenaline kit®
Good quality of life	8 (30.8%)
Average quality of life	13 (50%)
Poor quality of life	5 (19.2%)
Total	26 (66.66%)
P-value	0.503

the quality of life ranging from good to average, even in the other clinical presentations. The quality of life among those who were prescribed adrenaline kits was predominantly average.

There was no significant association between any of the variables and quality of life in this sample.

Discussion

The quality of life of children diagnosed with food allergy has been the subject of studies in recent years, leading to the development of many questionnaires as a tool to assess the impact of the disease and its treatment on the individual and those around him.

Generic questionnaires assess health-related quality of life using four basic domains (physical, psychological, social relationships, and the environment), allowing comparisons between groups of healthy individuals and those with different diseases.[13,14] Avery et al., for example, compared a group of peanut-allergic children with another group of children with insulin-dependent diabetes mellitus. The incidence and level of anxiety were higher in the peanut allergy group.[15] Calsbeek,[16] in turn, compared 98 food allergy patients with a group of 758 patients with chronic gastrointestinal diseases, finding that children and adolescents in the former group suffered a greater daily impact at school and in their recreational activities than the latter group. A Dutch study also compared general quality of life scores among individuals with food allergy, irritable bowel syndrome, diabetes mellitus, rheumatoid arthritis, and asthma. The quality of life of the food allergy group was worse than in the diabetes mellitus group and better than in the asthma, rheumatoid arthritis, and irritable bowel syndrome groups.[16]

The results of studies based on a generic assessment of quality of life suggest that the emotional effects observed in patients with food allergies are difficult to compare with those of individuals with other chronic diseases. Certain characteristics of patients with food allergies can lead to higher degrees of anxiety, although they seem to have less impact on their socialization than in those with non-episodic chronic illnesses.[5,17]

Studies on quality of life in food allergy patients have shown that certain specific factors can affect daily life, such as adrenaline prescription, history of anaphylaxis, and perceived responsibility for safeguarding one's own health. In that regard, DunnGalvin et al.[9] developed two quality of life questionnaires, one for children aged 0-12 years and another for adolescents aged 12-18 years. The questionnaires were prepared at University College Cork, Ireland, in five stages: the first involved the enumeration of items and content that precisely capture the concerns of parents, which was made possible through surveys of support groups, listening to experts, and a literature review. Clinical impact methodology was then applied to reduce the number of items in the questionnaire by assessing the frequency (number of parents endorsing each particular item), importance (mean scores given by parents for each question), and global importance (frequency vs. importance) of each item. In the third stage, the items were analyzed to determine the questionnaire scales, which were divided into 3 domains: emotional impact, food anxiety, and social and dietary limitations. In step 4, the questionnaire was validated using the Child Health Questionnaire and the Food Allergy Independent Measure. The fifth and final stage was cultural validation: the questionnaire was applied to patients at Duke University in the United States.[9,18]

The importance of multidisciplinary action (pediatrician, allergist, nutritionist, and psychologist) in food allergy treatment has been progressively highlighted,[19] especially the role of the nutritionist in the search for better quality of life for patients and their families/caregivers.[9,20,21] According to the Italian Society of Pediatric Nutrition and the Italian Society of Pediatric Allergy and Immunology, it is essential for children undergoing exclusion diets to be regularly monitored by a nutritionist,[19] with scheduled periodic reassessments to check nutritional needs, age-imposed adaptations, and diet adherence.[19] The follow-up plan should be based on age and growth pattern.[22] Thus, the nutritionist has a central role in supplying nutrients restricted by the diet (remembering that each age group requires special attention to certain nutrients), in addition to helping parents plan meals, which reduces anxiety and improves quality of life.[22]

Food allergies can also trigger psychological disorders in patients and their families.[23] The constant fear of anaphylactic reactions and the need for vigilance to prevent exposure to allergens create tension and are predictors of distress.[7] Ravid et al. demonstrated that such patients and their families are often more anxious and distressed and have poorer quality of life than the general population.[5]

Thus, this study sought to determine the quality of life and outline the psychological profile of the included patients. Regarding quality of life, no significant association was found among the variables, unlike internationally published data, in which there is an association between improved quality of life in food allergy patients and follow-up with a nutritionist, adrenaline prescription and injection training, and follow-up time at the service. Our small sample size (77 patients), the short follow-up period and, consequently, the number of times the questionnaire was applied might explain these divergent results, in addition to highlighting the need for prolonged nutritional support for patients at our Food Allergy Clinic. Moreover, our study did not assess whether quality of life varied according to the allergenic food or whether multiple food allergies intensify the negative effects on quality of life.

Our results also highlighted the patients' need for psychological support, although our clinic, unfortunately, does not provide such a service. According to the available data, this contributes to the fact that 59.7% of the sample has average or poor quality of life.

Conclusions

The quality of life questionnaire is an important monitoring tool for patients diagnosed with food allergy because it allows individualization of their profile and highlights factors that negatively impact their daily well-being.

Although published studies point to a direct association between certain variables and improved quality of life in this population, we did not find one, but rather a need for greater psychological support for patients followed at our Food Allergy Clinic.

Studies involving larger populations over a prolonged follow-up period should be encouraged in an effort to explore and identify other variables capable of improving therapeutic interventions and, consequently, the quality of life of children with food allergies.

Annex 1

Food Allergy Quality of Life Questionnaire for children 0 to 12 years old

ANEXO 1

Questionário de Qualidade de Vida na Alergia Alimentar

Crianças de 0 a 12 anos

Resposta dos pais

(FAQoL-PF)

Instruções aos Pais

- A seguir são situações sugeridas pelos pais que afetam a qualidade de vida de seus filhos devido a alergia alimentar.
- Favor indicar **qual o impacto** cada situação tem na **qualidade de vida de seu(sua) filho(a)** marcando um X nas opções numeradas de 0 a 6.

Opções de resposta

0 = nenhum
1= um pouco
2 = levemente
3 = moderado
4 = muito
5 = bastante
6 = extremo

Esse questionário é anônimo e será identificado por um código numérico, preservando sua identidade.

Há 4 seções neste questionário : **A, B, C e D.**

Se seu(sua) filho(a) tem de **0 a 3 anos**, favor responder a **seção A**
Se seu(sua) filho(a) tem de **4 a 6 anos,** favor responder **Seção A e B**
Se seu(sua) filho(a) tem **7 anos ou mais**, favor responder **Seção A, B e C**.

Código:

SEÇÃO A : para todas as idades

	Por causa da alergia alimentar, o(a) meu(minha) filho(a) se sente	Nenhum 0	1	2	3	4	5	Extremo 6
1	Ansioso(a) e preocupado(a) ao comer	□	□	□	□	□	□	□
2	Diferente das outras crianças	□	□	□	□	□	□	□
3	Frustrado(a) por não poder comer as comidas que quer	□	□	□	□	□	□	□
4	Com medo de experimentar comidas novas	□	□	□	□	□	□	□
5	Incomodado(a) com o fato de que eu esteja preocupado(a) com a possibilidade dele(a) ter uma reação com o alimento	□	□	□	□	□	□	□

	Por causa da alergia alimentar, meu(minha) filho(a)……	Nenhum 0	1	2	3	4	5	Extremo 6
6	Passa mal (fisicamente)	□	□	□	□	□	□	□
7	Apresenta distúrbios emocionais	□	□	□	□	□	□	□
8	Tem poucas opções de alimentos para comer	□	□	□	□	□	□	□

	Por causa da alergia alimentar, meu(minha) filho(a) tem sido prejudicado(a) por……	Nenhum 0	1	2	3	4	5	Extremo 6
9	Receber mais atenção do que as outras crianças da idade dele(a)	□	□	□	□	□	□	□
10	Ter que amadurecer mais rápido que as outras crianças da idade dele(a)	□	□	□	□	□	□	□
11	Ter seu ambiente mais limitado que as outras crianças da idade dele(a)	□	□	□	□	□	□	□

	Por causa da alergia alimentar, o ambiente social do(a) meu(minha) filho(a) é restrito devido a limitações em……..	Nenhum 0	1	2	3	4	5	Extremo 6
12	Encontrar restaurantes seguros em que possamos ir em família	□	□	□	□	□	□	□
13	Encontrar locais de férias que possamos ir tranquilamente em família	□	□	□	□	□	□	□
14	Nas atividades escolares de outras pessoas (como dormir fora de casa, festas, brincar, etc.)	□	□	□	□	□	□	□

SEÇÃO B: somente para crianças com idade de 4 a 12 anos

Código:

	Por causa da alergia alimentar, a participação do(a) meu(minha) filho(a) é limitada……..	Nenhum 0	1	2	3	4	5	Extremo 6
15	Na escola, quando envolve atividades ou eventos relacionados a comida (lanches, festas etc.)	□	□	□	□	□	□	□

	Por causa da alergia alimentar, meu(minha) filho(a) se sente……	Nenhum 0	1	2	3	4	5	Extremo 6
16	Ansioso(a) quando vai a lugares diferentes	□	□	□	□	□	□	□
17	Incomodado(a) com o fato de ter que ser cuidadoso com o que vai comer	□	□	□	□	□	□	□
18	'Excluído(a)' de atividades envolvendo comida	□	□	□	□	□	□	□
19	Chateado(a) que os passeios da família são limitados	□	□	□	□	□	□	□
20	Preocupado(a) em comer, acidentalmente, um alimento que possa causar alergia nele(a)	□	□	□	□	□	□	□
21	Ansioso(a) quando se alimenta com adultos ou crianças que não conhece	□	□	□	□	□	□	□
22	Frustrado(a) pelas limitações da sua vida social	□	□	□	□	□	□	□

	Por causa da alergia alimentar, meu(minha) filho(a)……	Nenhum 0	1	2	3	4	5	Extremo 6
23	É mais ansioso(a) do que as outras crianças da mesma idade	□	□	□	□	□	□	□
24	É mais cuidadoso(a) que as outras crianças da mesma idade	□	□	□	□	□	□	□
25	Menos confiante em situações sociais que as outras crianças da mesma idade	□	□	□	□	□	□	□
26	Deseja não ter mais alergia alimentar	□	□	□	□	□	□	□

SEÇÃO C : somente para crianças de 7 a 12 anos

Código:

	Por causa da alergia alimentar, meu(minha) filho(a) sente se……	Nenhum 0	1	2	3	4	5	Extremo 6
27	Preocupado(a) com o seu futuro (oportunidades, relacionamentos)	□	□	□	□	□	□	□
28	Preocupado(a) com o fato das pessoas não entenderem a gravidade de sua alergia alimentar	□	□	□	□	□	□	□
29	Preocupado(a) com a pequena quantidade de informação nos rótulos de produtos	□	□	□	□	□	□	□
30	Limitado(a) pela alergia alimentar	□	□	□	□	□	□	□

Annex 2

Food Allergy Quality of Life Questionnaire for adolescents 12 to 18 years old

ANEXO 2

QUESTIONÁRIO DE QUALIDADE DE VIDA

EM ALERGIA ALIMENTAR 12 a 18 ANOS

Instruções

- As perguntas abaixo estão relacionadas a situações que afetam a qualidade de vida segundo a opinião de adolescentes portadores de alergia alimentar.
- Favor indicar **qual o impacto** de cada situação na **sua qualidade de vida,** marcando um "X" em uma das opções numeradas de 0 a 6.
- Se a situação não tiver **nenhum impacto**, favor marcar **0 (sem impacto).**
- **Este questionário é anônimo e será identificado por um código numérico, preservando a sua identidade.**

Escolha da resposta	Exemplo de resposta
0 = Sem impacto	
1 = Um pouco de impacto	Essa situação tem impacto na minha vida?
2 = Algum impacto	Sim, tem muito impacto na minha vida.
3 = Impacto	
4 = Um pouco mais de impacto	
5 = Muito impacto	
6 = Impacto extremo	

	Pergunta	0	1	2	3	4	5	6
	Devido a alergia alimentar, eu me sinto…							
	Diferente das outras crianças						X	

Código:

SEÇÃO A - 1ª PARTE: O impacto da Alergia Alimentar

	Por causa da alergia alimentar, eu me sinto…… (Nenhum → Extremo)	0	1	2	3	4	5	6
1	Ansioso(a) e preocupado(a) ao comer	□	□	□	□	□	□	□
2	Diferente das outras crianças	□	□	□	□	□	□	□
3	Frustrado(a) por não poder comer as comidas que quero	□	□	□	□	□	□	□
4	Com medo de experimentar comidas novas	□	□	□	□	□	□	□
5	Incomodado(a) com o fato de minha mãe ou meu pai estarem preocupados com a possibilidade de eu ter uma reação alimentar	□	□	□	□	□	□	□

	Por causa da alergia alimentar, …… (Nenhum → Extremo)	0	1	2	3	4	5	6
6	Me sinto mal	□	□	□	□	□	□	□
7	Me sinto irritado(a) (de saco cheio)	□	□	□	□	□	□	□
8	Não tenho muitas opções de alimentos para comer	□	□	□	□	□	□	□

	Por causa da alergia alimentar, eu não gosto de…….. (Nenhum → Extremo)	0	1	2	3	4	5	6
9	Receber mais atenção do que outros meninos(as) da minha idade	□	□	□	□	□	□	□
10	Ter de amadurecer mais rápido que outros(as) meninos(as) da minha idade	□	□	□	□	□	□	□
11	Ter que tomar mais cuidado no dia a dia do que outros(as) meninos(as) da minha idade	□	□	□	□	□	□	□
12	Ter que carregar minha adrenalina (ou anti-alérgico) para todo lugar que vou	□	□	□	□	□	□	□

	Por causa da alergia alimentar, tenho problemas em….. (Nenhum → Extremo)	0	1	2	3	4	5	6
13	Encontrar restaurantes seguros que eu possa ir com meus amigos e familiares	□	□	□	□	□	□	□
14	Escolher locais de férias que eu possa ir tranquilamente com meus amigos	□	□	□	□	□	□	□
15	Atividades sociais na casa dos outros (*dormir fora, festas, refeições*)	□	□	□	□	□	□	□
16	Eventos escolares que envolvem comida (*recreio, festa da turma*)	□	□	□	□	□	□	□

	Por causa da alergia alimentar, eu me sinto…… (Nenhum → Extremo)	0	1	2	3	4	5	6
17	Ansioso(a) quando vou a locais diferentes	□	□	□	□	□	□	□
18	Incomodado(a) com o fato de ter de ser cauteloso(a) com a comida	□	□	□	□	□	□	□
19	Excluído(a) de atividades envolvendo comida	□	□	□	□	□	□	□
20	Chateado(a) que os passeios da família (comer fora, celebrações) são limitados, devido a minha alergia alimentar	□	□	□	□	□	□	□
21	Preocupado(a) em comer acidentalmente um alimento que possa me causar alergia	□	□	□	□	□	□	□
22	Ansioso(a) quando me alimento com adultos e crianças que não conheço	□	□	□	□	□	□	□
23	Frustrado(a) pelas limitações da minha vida social	□	□	□	□	□	□	□

	Por causa da alergia alimentar, eu me sinto …… (Nenhum → Extremo)	0	1	2	3	4	5	6
24	Mais ansioso(a) do que as outros meninos(as) da minha idade	□	□	□	□	□	□	□
25	Mais cuidadoso(a) do que as outros meninos(as) da minha idade	□	□	□	□	□	□	□
26	Menos confiante do que as outros meninos(as) da minha idade	□	□	□	□	□	□	□
27	Na expectativa que minha alergia alimentar acabe.	□	□	□	□	□	□	□

	Por causa da alergia alimentar, eu me sinto…… (Nenhum → Extremo)	**0**	**1**	2	3	4	5	6
28	Preocupado(a) com meu futuro (relacionamentos, oportunidades, etc.)	□	□	□	□	□	□	□
29	Preocupado(a) com o fato das pessoas não entenderem a gravidade da minha alergia	□	□	□	□	□	□	□
30	Preocupado(a) com a pequena quantidade de informação nos rótulos dos produtos	□	□	□	□	□	□	□
31	Preocupado(a) com a possibilidade de ter uma reação ao beijar alguém que eu goste	□	□	□	□	□	□	□
32	Preocupado(a) que a alergia alimentar limita a minha vida em geral	□	□	□	□	□	□	□

Annex 3

Answer sheets

ANEXO 3

QQV Folha de Respostas (0-3 anos)

1. Impacto emocional Domínio		2. Ansiedade alimentar Domínio		3. Limitações sociais e dietéticas Domínio	
Pergunta	**Ponto (0-6)**	**Pergunta**	**Ponto (0-6)**	**Pergunta**	**Ponto (0-6)**
Coloque os pontos de cada pergunta abaixo		Coloque os pontos de cada pergunta abaixo		Coloque os pontos de cada pergunta abaixo	
Q. 2		**Q. 1**		**Q. 3**	
Q. 6		**Q. 4**		**Q. 8**	
Q. 7		**Q. 5**		**Q. 12**	
Q. 9				**Q. 13**	
Q. 10				**Q. 14**	
Q. 11					
Total		**Total**		**Total**	
Total / 6 = Pontos do domínio impacto emocional (IE)		Total / 3 = Pontos do domínio ansiedade alimentar (AA)		Total / 5 = pontos do domínio limitações sociais e dietéticas (LSD)	
Pontos do domínio IE=		**Pontos do domínio AA=**		**Pontos do domínio LSD =**	

QQV Score final = (Pontos do domínio IE+ Pontos do domínio AA+Ponto do domínio LSD) / 3

QQV Score final = (_____ + _____ + _____) / 3 = _____

QQV Folha de Respostas (4-6 anos)

1. Impacto emocional Domínio		2. Ansiedade alimentar Domínio		3. Limitações sociais e dietéticas Domínio	
Pergunta	**Ponto (0-6)**	**Pergunta**	**Ponto (0-6)**	**Pergunta**	**Ponto (0-6)**
Coloque os pontos de cada pergunta abaixo		Coloque os pontos de cada pergunta abaixo		Coloque os pontos de cada pergunta abaixo	
Q. 2		**Q. 1**		**Q. 3**	
Q. 6		**Q. 4**		**Q. 8**	
Q. 7		**Q. 5**		**Q. 12**	
Q. 9		**Q. 16**		**Q. 13**	
Q. 10		**Q. 17**		**Q. 14**	
Q. 11		**Q. 20**		**Q. 15**	
Q. 23		**Q. 21**		**Q. 18**	
Q. 24				**Q. 19**	
Q. 25				**Q. 22**	
Q. 26					
Total		**Total**		**Total**	
Total / 10 = Pontos do domínio impacto emocional (IE)		Total / 7 = Pontos do domínio ansiedade alimentar (AA)		Total / 9 = pontos do domínio limitações sociais e dietéticas (LSD)	
Pontos do domínio IE=		**Pontos do domínio AA=**		**Pontos do domínio LSD =**	

QQV Score final = (Pontos do domínio IE+ Pontos do domínio AA+Ponto do domínio LSD) / 3

QQV Score final = (_____ + _____ + _____) / 3 = _____

QQV Folha de Respostas (7-12 anos)

Impacto Emocional Domínio		Ansiedade alimentar Domínio		Limitações sociais e dietéticas Domínio	
Pergunta	**Ponto (0-6)**	**Pergunta**	**Ponto (0-6)**	**Pergunta**	**Ponto (0-6)**
Coloque os pontos de cada pergunta abaixo		Coloque os pontos de cada pergunta abaixo		Coloque os pontos de cada pergunta abaixo	
Q. 2		**Q. 1**		**Q. 3**	
Q. 6		**Q. 4**		**Q. 8**	
Q. 7		**Q. 5**		**Q. 12**	
Q. 9		**Q. 16**		**Q. 13**	
Q. 10		**Q. 17**		**Q. 14**	
Q. 11		**Q. 20**		**Q. 15**	
Q. 23		**Q. 21**		**Q. 18**	
Q. 24		**Q. 29**		**Q. 19**	
Q. 25				**Q. 22**	
Q. 26					
Q. 27					
Q. 28					
Q. 30					
Total		**Total**		**Total**	
Total / 13 = Pontos do domínio impacto emocional (IE)		Total / 8 = Pontos do domínio ansiedade alimentar (AA)		Total / 9 = pontos do domínio limitações sociais e dietéticas (LSD)	
Pontos do domínio IE=		**Pontos do domínio AA=**		**Pontos do domínio LSD =**	

QQV Score final = (Pontos do domínio IE+ Pontos do domínio AA+Ponto do domínio LSD) / 3

QQV Score final = (_____ + _____ + _____) / 3 = _____

QQV Folha de Respostas (12-18 anos)

1. Impacto emocional Domínio		2. Ansiedade alimentar Domínio		3. Limitações sociais e dietéticas Domínio	
Pergunta	**Ponto (0-6)**	**Pergunta**	**Ponto (0-6)**	**Pergunta**	**Ponto (0-6)**
Coloque os pontos de cada pergunta abaixo		Coloque os pontos de cada pergunta abaixo		Coloque os pontos de cada pergunta abaixo	
Q. 2		**Q. 1**		**Q. 3**	
Q. 6		**Q. 4**		**Q. 8**	
Q. 7		**Q. 5**		**Q. 12**	
Q. 9		**Q. 17**		**Q. 13**	
Q. 10		**Q. 18**		**Q. 14**	
Q. 11		**Q. 20**		**Q. 15**	
Q. 24		**Q. 22**		**Q. 16**	
Q. 25		**Q. 30**		**Q. 19**	
Q.26				**Q.21**	
Q. 27				Q.23	
Q. 28				Q31	
Q. 29					
Q. 32					
Total		**Total**		**Total**	
Total / 13 = Pontos do domínio impacto emocional (IE)		Total / 8 = Pontos do domínio ansiedade alimentar (AA)		Total / 11 = pontos do domínio limitações sociais e dietéticas (LSD)	
Pontos do domínio IE=		**Pontos do domínio AA=**		**Pontos do domínio LSD =**	

QQV Score final = (Pontos do domínio IE+ Pontos do domínio AA+Ponto do domínio LSD) / 3

QQV Score final = (_____ + _____ + _____) / 3 = _____

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Vasomotor rhinitis and rhinorrhea: a possible role for the anticholinergic effect of amitriptyline

Rinite vasomotora e rinorreia: um possível papel para o efeito anticolinérgico da amitriptilina

Francisco Machado Vieira[1]

ABSTRACT

Background: Vasomotor rhinitis (VMR), also referred to as idiopathic rhinitis, is a type of nonallergic rhinitis. It can often be triggered by changes in temperature, especially with cold air and other airway irritants. Immunoglobulin E (IgE) levels and nasal cytograms are normal, and inhalant skin tests are negative. The etiology may be associated with dysregulation of the sympathetic and parasympathetic nervous systems in the nasal mucosa, with increased rhinorrhea and nasal obstruction. **Objective:** To evaluate the efficacy of amitriptyline in the control of VMR-related rhinorrhea. **Method:** We retrospectively evaluated 110 patients with VMR, of whom 12 (11%) had profuse rhinorrhea for more than 1 year, not completely controlled with nasal corticosteroids. In these 12 patients, rhinorrhea was treated with amitriptyline, a tricyclic antidepressant with intense anticholinergic activity, at a daily dose of 25 mg/50 mg. **Results:** Patients were evaluated using a symptom scale (modified from Wilson AM): 0 = absent; 1 = mild, well tolerated; 2 = discomfort interfering with concentration; and 3 = severe intensity interfering with sleep and concentration. Ten patients had grade 3 symptoms, and 2 had grade 2 symptoms. The score decreased to grade 0-1 after 4-6 weeks of amitriptyline use for reflex symptoms in the morning and at night. **Conclusion:** Further controlled studies with a larger sample size are needed to confirm the pharmacological effect of amitriptyline on VMR-related rhinorrhea.

Keywords: Vasomotor rhinitis, amitriptyline, rhinorrhea.

RESUMO

Introdução: A rinite vasomotora (RVM), também denominada idiopática, é um tipo de rinite não alérgica. Pode ser muitas vezes ativada por mudanças de temperatura, especialmente com o ar frio e outras irritantes de vias aéreas. A dosagem de IgE e o citograma nasal são normais, e os testes de inalantes são negativos. A etiologia pode estar associada à desregulação de nervos simpáticos e parassimpáticos da mucosa nasal, onde aumenta a rinorreia e a obstrução nasal. **Objetivo:** Avaliar a eficácia da amitriptilina no controle da rinorreia vasomotora. **Método:** Através de estudo retrospectivo, avaliaram-se pacientes com RVM (n = 110), no qual um grupo de n = 12 (11%) apresentava rinorreia profusa há mais de um ano, não controlada, na sua totalidade, com corticosteroide nasal. Usou-se a amitriptilina, um antidepressivo tricíclico, com intensa atividade anticolinérgica com dose de 25 mg/50 mg diária para a rinorreia nesses pacientes. **Resultados:** Foram avaliados através de uma escala de sintomas (modificada de Wilson AM): 0 = ausente, 1 = leve, bem tolerado, 2 = desconforto interferindo com a concentração, 3 = forte intensidade interferindo no sono e na concentração. Dez pacientes catalogados apresentaram sintomas no grau 3, e dois, no grau 2. A pontuação foi reduzida para grau 0-1 após 4-6 semanas com o uso de amitriptilina por sintomas reflexivos matinais e noturnos. **Conclusão:** Futuros estudos controlados e com maior número de pacientes seriam necessários para confirmação do efeito farmacológico da amitriptilina na rinorreia da RVM.

Descritores: Rinite vasomotora, amitriptilina, rinorreia.

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Introduction

Vasomotor rhinitis (VMR) is a type of nonallergic rhinitis that may be acute or chronic. It can often be triggered by changes in temperature and humidity, especially cold dry air, airway irritants, strong odors including tobacco smoke, and exercise.[1]

VMR is often a diagnosis of exclusion and commonly referred to as idiopathic rhinitis.[1,2] This denomination seems to be more appropriate than VMR because of the nonspecific triggers and the yet not fully elucidated mechanism. Family history of allergy and allergen-specific immunoglobulin E (IgE) testing are negative. Total serum IgE levels and nasal cytograms are normal, with few or no eosinophils.[2]

Although the etiology of VMR is not well understood, it is believed to be associated with dysregulation of the sympathetic, parasympathetic, and nociceptive nerves present in the nasal mucosa. The parasympathetic nervous system plays an important role in the response to external stimuli. The imbalance between mediators results in increased vascular permeability and mucus secretion from the submucosal glands.[3] Acetylcholine is the primary parasympathetic neurotransmitter that regulates mucus secretion and rhinorrhea.

The acronym VMR has been proposed by some authors and is currently used in clinical practice; therefore, VMR is used in this text rather than idiopathic rhinitis. Although the latter term is recommended by the IV Brazilian Consensus on rhinitis (2017), it is not universally accepted, since high levels of eosinophils and mast cells may be present, so the term VMR continues to be used.[4]

VMR accounts for approximately 71% of cases of nonallergic rhinitis. A worldwide prevalence of more than 200 million people is estimated, despite the weakness of epidemiological studies.[5]

VMR has an onset in adulthood, usually between 30 and 60 years of age. It is more common in women (58%-71%) and can last a lifetime.[5-7]

Profuse rhinorrhea may alter the patient's quality of life both physically and psychosocially if not properly treated. VMR symptoms may vary, consisting mainly of nasal obstruction and increased clear secretion, postnasal drip, and intermittent rhinorrhea. There are 2 subtypes, one with predominant nasal obstruction, and the other with predominant profuse rhinorrhea.[2] Sneezing and pruritus are less common, whereas cough may appear as an important component of VMR.[2,4]

Climate changes, including cold air, can trigger VMR. In Brazil, VMR has been mostly observed and is possibly more prevalent in the South region due to a low-temperature harsh winter season, followed by a spring season with a prolonged period of cold mornings and nights.

Treatment should be based on symptoms. The combination of a topical corticosteroid and an H1 antihistamine, such as azelastine nasal spray, may be used in patients with predominant rhinorrhea/nasal obstruction, whereas ipratropium bromide (IB), an anticholinergic agent, is recommended for those with predominant rhinorrhea.[8]

Amitriptyline is a medication approved for the treatment of depression in adults. It is a tricyclic antidepressant, with a high affinity for alpha-adrenergic receptor binding to histamine H1 and muscarinic (M1 subtype) receptors. It has a half-life of 10-28 hours and is metabolized into nortriptyline.[9] Its anticholinergic effects include blurred vision, dry mouth, tachycardia, angle-closure glaucoma, and urinary retention. The latter effect may be beneficial to treat patients with enuresis, as listed on the package insert. The pharmacological activity of amitriptyline might support its off-label use in the treatment of poorly controlled rhinorrhea.

The primary objective of this study was to retrospectively identify and analyze the use of amitriptyline in patients unresponsive to nasal corticosteroids for VMR-associated rhinorrhea.

Anticholinergic drugs for nonallergic rhinitis

Anticholinergic drugs inhibit the binding of acetylcholine to muscarinic receptors and can be used topically or systemically.[4] The parasympathetic nervous system contributes to the pathophysiology of multiple forms of rhinitis, and its stimulation leads to activation of the gland that produces watery nasal secretion, which translates into anterior and posterior rhinorrhea.[1]

It has been shown that the transient receptor potential vanilloid 1 (TRPV1)-substance P (SP) nociceptive signaling pathway (cation channel subfamily) is upregulated in patients with idiopathic rhinitis and reduced after treatment with intranasal capsaicin.[10]

Based on its anticholinergic activity, IB nasal spray has been approved for the treatment of rhinorrhea in

allergic and nonallergic rhinitis.[11,12] In Brazil, it has been off the market for several years.

Azelastine hydrochloride nasal spray 0.1% is a second-generation antihistamine with pharmacological effects on inflammatory mediators. It improves both allergic rhinitis and VMR symptoms.[4] When combined with fluticasone nasal spray, it provides greater symptom relief.[13]

First-generation oral antihistamines are poorly selective for H1 receptors and can cause anticholinergic effects by inhibiting muscarinic receptors, which could be useful in VMR. However, because they cross the blood-brain barrier, sedation may occur, affecting daily activities and interfering with quality of life.[14]

Amitriptyline may be a promising candidate for potential control of VMR-associated watery rhinorrhea.

Patients and methods

We retrospectively reviewed the clinical records of 110 patients with a diagnosis of VMR made from 2003 to 2021 at an Allergy and Immunology Clinic in Caxias do Sul, southern Brazil. The diagnosis was based on characteristic clinical features and anterior rhinoscopy (examination of the mucosa, septum, and nasal turbinates), combined with skin prick tests for aeroallergens when the results were negative. The allergens included in the test panel were *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, dog and cat epithelium, *Penicillium*, *Cladosporium*, *Lolium pollen*, and grass mix, using saline and histamine as negative and positive controls, respectively (10 mg/mL).

We included 12 patients (7 men) with VMR, assessed for the first time, from various clinics, with symptoms for more than 1 year. Mean patient age was 54 years, ranging from 26 to 80 years. The most common symptom was intermittent profuse rhinorrhea, not completely controlled with daily use of nasal corticosteroids for months.

Patients were evaluated with a modified 4-point symptom scale for rhinorrhea, with scores as follows: 0 = no rhinorrhea; 1 = mild, well tolerated not interfering with sleep or daily activities; 2 = discomfort interfering with concentration; and 3 = severe intensity interfering with sleep and daily activities.[14] Ten patients had grade 3 symptoms, and 2 had grade 2 symptoms. Nasal obstruction was rated as absent or mild (grade 0-1) by 11 patients (92%).

Amitriptyline (25-50 mg/day) was administered at night. We excluded risk factors such as patients with a history of seizures, impaired liver function, urinary retention, narrow-angle glaucoma or increased intraocular pressure, and cardiovascular disorders.

Amitriptyline was administered for 4-6 weeks and then at face-to-face medical visits for 8 consecutive weeks. Patients received information about the drug, including the most common side effects, such as dry mouth, reduced saliva production, and potential sedation. After being fully informed of the effects of the drug, they consented to the use of amitriptyline to try to control their "persistent bothersome rhinorrhea," since this is an off-label indication.

Results

All 12 patients had symptoms of profuse watery rhinorrhea, rated as grade 3 by 10 patients and as grade 2 by 2 patients.

After 4-6 weeks of amitriptyline 25-50 mg/day, both watery rhinorrhea and postnasal drip reduced significantly. The symptom score decreased to grade 0-1 according to morning and evening reflective symptoms.[6]

Two patients were excluded from the study due to adverse effects: one had constipation, and the other developed tachycardia and arrhythmia.

Mild daytime sleepiness was reported by patients receiving a dose of 50 mg/day, which was tapered over subsequent weeks with early evening administration.

The results are shown in Table 1.

Discussion

Intranasal corticosteroids are effective in treating several forms of nonallergic rhinitis, including eosinophilic nonallergic rhinitis.[4] The fact that all patients had previously used nasal corticosteroids ruled out the diagnosis of eosinophilic nonallergic rhinitis, which could be a selection bias. Treatment with fluticasone furoate has not been effective in alleviating the symptoms of patients with allergic rhinitis due to temperature changes/cold, and it has been suggested that a distinct group of patients with VMR may be refractory to corticosteroids.[15] This is consistent with the subgroup included in the present study, in which 11% of a total of 110 patients with VMR had profuse

Table 1
Rhinorrhea in vasomotor rhinitis. Assessment with amitriptyline administration (mg/day)

Patient	Age	Sex	Pre-treatment symptoms Rhinorrhea	Amitriptyline dose (mg/day) Rhinorrhea	Post-treatment symptoms Adverse	Patients excluded due to adverse effects
1	45	F	3	25	1	–
2	33	M	3	25	0	–
3	58	M	3	25	0	*
4	61	F	3	50	1	–
5	55	F	2	25	0	–
6	56	M	3	25	0	–
7	26	F	2	25	0	–
8	42	M	3	25	0	–
9	67	M	3	50	0	–
10	63	F	3	25	0	–
11	80	M	3	50	0	–
12	67	M	3	25	0	**

Symptom score:

0 = None.
1 = Mild, well tolerated not interfering with sleep or daily activities.
2 = Discomfort interfering with concentration.
3 = Severe intensity interfering with sleep and daily activities.

Legend: – not detected, * constipation, ** tachycardia/arrhythmia.

Modified from Wilson AM et al.[15]

rhinorrhea that was not completely controlled with nasal corticosteroids for months.

During the study period, no anticholinergic drug such as IB nasal spray was available in Brazil. The same occurred intermittently with azelastine nasal spray, which can be used in VMR. First-generation antihistamines with anticholinergic properties were available, but they were not indicated due to their side effects, such as daytime sedation.

We were able to evaluate the use of a potent anticholinergic drug such as amitriptyline for rhinorrhea, in line with its indication for nocturnal enuresis as listed on the package insert.[9]

A characteristic shared by our patients was that they had no or minimal nasal obstruction according to the symptom scale (grade 0-1).

Conclusion

Limitations of this study include those inherent in a retrospective data analysis and the small sample size, obtained from a subgroup of patients unresponsive to nasal corticosteroids for the management of rhinorrhea. Also, psychosocial assessment was not performed and anxiety or depression scales were not used. Amitriptyline may influence the reflective symptom scores due to its pharmacological effect on these conditions. Amitriptyline should be considered an option as it is a low-cost, accessible medication provided through the Brazilian public health system without patient charges.

Further controlled studies with a larger sample size are required to better evaluate the use of amitriptyline in VMR, especially in patients with predominant rhinorrhea.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Melkersson-Rosenthal syndrome as a differential diagnosis of lip swelling

Síndrome de Melkersson-Rosenthal como diagnóstico diferencial de edema labial

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ABSTRACT

Melkersson-Rosenthal syndrome is a rare condition characterized by the classic triad: orofacial edema, fissured tongue, and facial paralysis. Only 1 or 2 manifestations of the triad may be present for a prolonged time, making diagnosis difficult. It is called Miescher's cheilitis when the only manifestation is orofacial edema, with characteristic histology. The present report aims to alert to the diagnosis of Melkersson-Rosenthal syndrome in cases of chronic lip angioedema, with a review of the literature. A 40-year-old woman presented with lip swelling since the age of 23, with no regression of the swelling for 5 years, without pruritus or triggers. A fissured tongue was observed on physical examination. Complementary tests showed no abnormalities. Persistent orofacial edema, fissured tongue, lower lip biopsy showing chronic cheilitis (hyperkeratosis and perivascular lymphocytic infiltration) and the exclusion of differential diagnoses through complementary tests led to the diagnosis of Melkersson-Rosenthal syndrome. The patient was then referred to the Plastic Surgery Service, which recommended surgical removal of excess lip tissue. The diagnosis of the syndrome is essentially clinical. Treatment should be individualized, aiming to alleviate the clinical manifestations in each case. Multidisciplinary follow-up is important to minimize psychological damage and improve prognosis. Melkersson-Rosenthal syndrome can present as chronic lip angioedema and fissured tongue, without facial paralysis, which may delay the diagnosis, as in the present case. It is necessary to consider the syndrome to allow earlier diagnosis and management and to provide a better quality of life for these patients.

Keywords: Allergy and Immunology, angioedema, Melkersson-Rosenthal syndrome, facial paralysis.

RESUMO

A síndrome de Melkersson-Rosenthal é uma condição rara caracterizada pela tríade clássica: edema orofacial, língua fissurada e paralisia facial. Pode haver apenas uma ou duas manifestações por tempo prolongado, dificultando o diagnóstico. É denominada queilite de Miescher quando a única manifestação é o edema orofacial, com histologia característica. O presente relato tem como objetivo alertar para o diagnóstico da síndrome de Melkersson-Rosenthal em casos de angioedema labial crônico, com revisão da literatura. Mulher de 40 anos apresentando edema labial desde os 23 anos de idade, sem regressão há cinco anos, sem prurido, sem desencadeantes. Observou-se língua fissurada ao exame físico. Sem alterações aos exames complementares. O edema orofacial persistente, a língua fissurada, a biópsia de lábio inferior evidenciando queilite crônica (hiperqueratose e infiltração linfocítica perivascular) e a exclusão de diagnósticos diferenciais através de exames complementares permitiram o diagnóstico da síndrome de Melkersson-Rosenthal. A paciente foi então encaminhada à Cirurgia Plástica, que orientou retirada cirúrgica do excesso labial. O diagnóstico da síndrome é essencialmente clínico. O tratamento deve ser individualizado, visando o alívio das manifestações clínicas apresentadas em cada caso. É importante o acompanhamento multiprofissional tentando minimizar danos psicológicos e melhorar o prognóstico. A síndrome de Melkersson-Rosenthal pode apresentar-se como angioedema labial crônico e língua fissurada, sem paralisia facial, podendo retardar o diagnóstico, como no presente caso. É necessária a lembrança da síndrome para o diagnóstico e conduta mais precoce, para melhor qualidade de vida destes pacientes.

Descritores: Síndrome de Melkersson-Rosenthal, angioedema, paralisia facial, alergia e imunologia.

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Introduction

Lip swelling is a common complaint in the physician's office and is a symptom of several diseases, allergic or not. Researching the causes of orofacial edema is important to provide adequate treatment and patient guidance.

Melkersson-Rosenthal syndrome (MRS) was initially described in 1928 as facial edema by Melkersson. In 1931, Rosenthal added lingua plicata to the list of symptoms. In 1949, the syndrome was considered a neuromucocutaneous disorder characterized by a classic triad of orofacial edema, lingua plicata, and facial palsy.[1,2] Only 1 or 2 manifestations may be present for a prolonged time, making it difficult to diagnose this condition. The presence of orofacial edema alone, with characteristic histology, characterizes Miescher's granulomatous cheilitis.[2] The pathogenesis of MRS is still poorly understood, but it is believed to be multifactorial, involving allergic, infectious, autoimmune, and hereditary causes.[3-6]

The objective of this study was to report the case of a patient diagnosed with MRS after 17 years of severe lip swelling and conduct a literature review to warn about the possible diagnosis of this condition.

This retrospective, clinical and laboratory, longitudinal study of medical records was conducted after the patient provided written informed consent. A literature review was conducted on MEDLINE/PubMed, Biblioteca Virtual em Saúde, and Google Scholar databases.

Case report

A 40-year-old female seamstress complained of lip swelling since she was 23 years old. The swelling would appear suddenly, usually every 4 months, with periods of complete remission in between. She reported having sought health services several times and being treated with oral corticosteroids, nonsteroidal anti-inflammatory drugs, and antihistamines on separate occasions, but without improvement of the condition. The episodes became more frequent, longer, and did not respond to treatment. The patient reported being discouraged by treatment failure and swelling recurrence and completely discontinued the treatment initially proposed. After pregnancy, the episodes of lip swelling became more frequent and, eventually, persistent.

She was referred to a specialized sector of a teaching hospital, where she complained of swelling in the upper and lower lips for 17 years, with no remission in the past 5 years (Figure 1). She denied the presence of urticaria, pruritus, fever, triggering factors or other complaints, as well as previous comorbidities or family history of swelling. On physical examination, she showed marked and asymmetric swelling of the lower and upper lips, with preserved sensitivity and no local hyperemia. In addition to labial angioedema, the examination revealed several fissures on the dorsum of the tongue that were attached to a central fissure, which the patient had never mentioned.

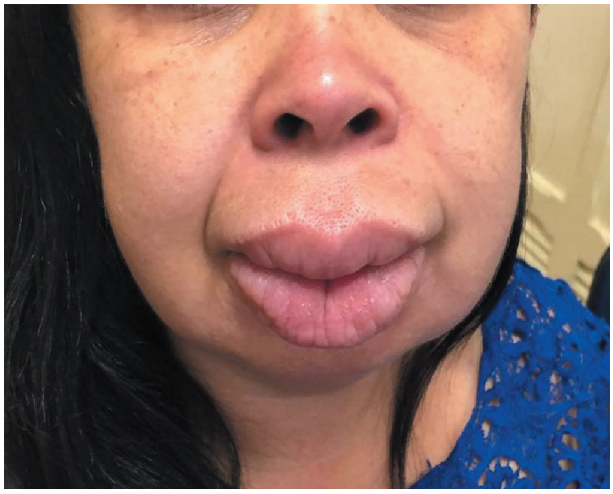

Figure 1
Patient with upper and lower lip swelling for 17 years: the most frequent form of Melkersson-Rosenthal Syndrome

Based on patient history and physical examination, the following diagnostic hypotheses were raised: MRS, hereditary angioedema, acquired angioedema, and adverse reaction to nonsteroidal anti-inflammatory drugs. The following laboratory tests were requested: CH50 320 U (reference range [RR] = 170-330), C3 147 mg/dL (RR = 67-149), C4 38 mg/dL (RR = 10-38), quantitative (16 mg/dL) and functional C1-esterase inhibitor (C1-INH) within the normal range (RR = 14-30), normal complete blood count, and absence of autoantibodies.

Lower lip biopsy showed hyperkeratosis, swelling, and mild perivascular lymphocytic infiltration, which characterize chronic cheilitis. Local infiltration with corticosteroids and use of dapsone were

recommended. The patient received a few applications and used the oral medication for 2 months irregularly. Due to treatment nonadherence and lack of improvement, she stopped attending medical appointments. She returned for follow-up 2 years later with permanent lip swelling, as well as weight loss, lack of appetite, and marked psychosocial impairment, with emotional lability and total social isolation.

The patient was referred to the plastic surgery department to evaluate the possibility of surgical correction to improve her quality of life. After evaluation, surgical removal of excess tissue was recommended, and the patient appeared to be motivated. She is currently in preoperative evaluation, awaiting the procedure.

Discussion

The patient only complained of lip swelling for 17 years. After lingua plicata was identified on clinical examination, the hypothesis of MRS was raised, and laboratory tests were requested to complement the investigation. The diagnosis of MRS is essentially clinical and based on the presence of 2 manifestations of the classic triad.[5] Cases that only present with orofacial edema require biopsy for the diagnostic confirmation of cheilitis, which is the most frequent monosymptomatic form of the syndrome, called Miescher's granulomatous cheilitis.[2-6]

The onset of MRS is more common in young adults, between the second and third decades of life,[3] as in the present case. It has an estimated incidence of 0.08% in the general population, but the number of cases is believed to be underreported.[4] MRS mostly affects women, but there are no differences between ethnicities.[3] The classic triad of orofacial edema, facial palsy, and lingua plicata is observed in only 8% to 25% of cases.[2,7]

In this syndrome, orofacial edema is painless, asymmetrical, nonpruritic, non-erythematous, and may affect the lip, gums, tongue, chin, cheeks, and even the periorbital region, with the upper lip being the most frequently affected part.[6,8] The swelling regresses rapidly in most cases. However, increased swelling recurrence decreases the chances of regression, and the swelling may become permanent, as in the present case.

Lingua plicata is a nonspecific sign observed in 20% to 77% of cases.[9] The fissures appear along the entire dorsal surface of the tongue and are attached to a single central fissure, as in the present case. Although bacterial and fungal infections are commonly associated with lingua plicata, the patient had no signs of infection.[9]

Peripheral facial nerve palsy in RMS is recurrent, of sudden onset, uni or bilateral, and is observed in 90% of cases,[8] with no difference between genders. It may occur alone years before or after orofacial edema, thus the diagnosis should be revised according to the evolution of the condition. Although the classic triad is well defined, signs and symptoms that suggest the involvement of other cranial nerves may be included in the diagnostic criteria: changes in ocular motility and functionality of salivary and lacrimal glands, hyperacusis, hyperhidrosis, and hypergeusia, as well as different ocular manifestations such as retrobulbar neuritis and blepharochalasis.[8] The patient in question did not have facial palsy or cranial nerve involvement during the 17 years of illness, which may have delayed the diagnosis.

Additional tests are required to exclude differential diagnoses such as hereditary angioedema, foreign body reaction, sarcoidosis, Crohn's disease, Wegener's vasculitis, amyloidosis, infections, Bell's palsy, orofacial herpes, contact dermatitis, and allergic reactions.[5,6] The patient in question showed no signs of infection. Autoimmune diseases, which may co-occur with MRS, were ruled out due to the absence of manifestations and autoreactive antibodies. The hypothesis of hereditary angioedema was ruled out by laboratory tests. Acquired angioedema due to C1-INH deficiency may be caused in particular by autoimmune or lymphoproliferative disorders, which were ruled out by clinical examination and laboratory tests.

Microscopy of MRS angioedema is characterized by a chronic inflammatory process, with noncaseating epithelioid granulomas, surrounding mononuclear infiltrate, Langerhans giant cells, and perivascular lymphoplasmacytic infiltrate.[1-3,5,10] In this report, the biopsy was relevant because it showed hyperkeratosis, edema, and perivascular lymphocytic infiltration, which are characteristic of chronic cheilitis.

The patient's clinical manifestations of recurrent and then persistent lip swelling, lingua plicata, and chronic cheilitis identified by biopsy allowed the diagnosis of MRS, even in the absence of facial palsy.

Anti-inflammatory drugs, especially oral or intralesional corticosteroids, methotrexate, and dapsone[10,12] are among the main treatments for MRS. However, they were unsuccessful in this patient. A surgical approach should be considered in case of deformed swelling with psychosocial impairment,[13,14] as in the present case. Recurrent treatment dropout by the patient shows the direct impact of psychological and emotional changes resulting from the physical appearance of progressive edema.

Given the impact of the diagnosis on quality of life, the need to recognize the clinical manifestations of MRS at an early stage and establish integrated follow-up for a better prognosis is extremely important. In addition to pharmacological therapy, multidisciplinary action involving dermatologists, plastic surgeons, otolaryngologists, physical therapists (in the case of paralysis), and follow-up with psychologists and psychiatrist to prevent psychosocial impairment is required.

Conclusion

In this case report, the patient had presented lip swelling for 17 years, which was initially recurrent and later became persistent, in addition to the clinical finding of lingua plicata (which was never reported by the patient). She was diagnosed with MRS. Lower lip biopsy showed changes that were consistent with chronic cheilitis, while laboratory tests ruled out differential diagnoses, contributing to the final diagnosis. The lack of facial palsy may have contributed to the late diagnosis, as well as the lack of perception of lingua plicata by the patient.

This report shows the importance of including MRS in the differential diagnosis of recurrent or persistent lip swelling accompanied by lingua plicata, even in the absence of facial palsy. Earlier diagnosis of the syndrome would have provided better quality of life for the patient.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Hypersensitivity pneumonitis in childhood

Pneumonite de hipersensibilidade na infância

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ABSTRACT

We report the clinical, epidemiological, and radiological features of hypersensitivity pneumonitis, a rare cause of respiratory failure in pediatrics. An 8-year-old male patient, from a rural area, was admitted to a tertiary care facility for fever, vomiting, dry cough, progressive dyspnea, anorexia, and weight loss for 15 days, associated with tachypnea, respiratory effort, hypoxia, and fine rales at the right base. Chest computed tomography showed ground-glass opacities, diffuse involvement, and predominantly centrilobular and acinar distribution, characteristic of hypersensitivity pneumonitis. In the review of living conditions and habits, the patient's guardian reported the presence of an aviary and interaction with birds of various species in the residence, supporting the presumptive diagnosis of hypersensitivity pneumonitis, after ruling out other causes of respiratory failure. Corticosteroid therapy was started with methylprednisolone 1 mg/kg/day for 7 days, followed by tapering over subsequent weeks. The patient's condition improved, and he was discharged home after receiving guidance on environmental control and the importance of removing the triggering antigens. Hypersensitivity pneumonitis is an uncommon syndrome in the pediatric population. It can lead to respiratory failure and pulmonary fibrosis and should therefore be considered in patients with a positive epidemiological history. Due to its rarity and similarity to other respiratory diseases, collecting data on patients' lifestyle habits is highlighted as an important diagnostic tool.

Keywords: Lung diseases, interstitial, child, respiratory insufficiency.

RESUMO

Neste relato descrevemos as características clínicas, epidemiológicas e radiológicas da pneumonite de hipersensibilidade, uma causa rara de insuficiência respiratória em pediatria. Paciente masculino, com 8 anos de idade, proveniente da zona rural, admitido em serviço terciário por quadro de febre, vômitos, tosse seca, dispneia progressiva, anorexia e perda de peso há 15 dias, associado a taquipneia, esforço respiratório, hipóxia e estertores finos em base direita. Tomografia computadoriza de tórax demonstrou opacidades com atenuações em vidro fosco, com comprometimento difuso e distribuição predominantemente centrolobular e acinar, característicos de pneumonite por hipersensibilidade. Na revisão das condições e hábitos de vida, foi relatado pela responsável do paciente a presença de um aviário e convívio com aves de várias espécies na residência, reforçando a hipótese diagnóstica, após descartadas outras causas de insuficiência respiratória. Iniciado corticoterapia com metilprednisolona 1 mg/kg/dia por 7 dias, seguido de redução progressiva nas semanas posteriores. Paciente evoluiu com melhora do quadro e alta hospitalar, após orientações sobre controle ambiental e importância do afastamento dos antígenos desencadeantes. A pneumonite por hipersensibilidade é uma síndrome incomum na população pediátrica, que pode levar à insuficiência respiratória e fibrose pulmonar, devendo ser considerada nos pacientes com epidemiologia positiva. Pela sua raridade e semelhança com outras infecções respiratórias, ressalta-se ainda a importância da coleta de dados sobre os hábitos de vida dos pacientes, destacando sua importância para a elucidação diagnóstica.

Descritores: Doenças pulmonares intersticiais, criança, insuficiência respiratória.

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Introduction

Hypersensitivity pneumonitis (HP), also referred to as extrinsic allergic alveolitis, is a complex syndrome involving a number of lung diseases, predominantly in the small airways.[1] It results from an immune reaction to an inhaled agent, particularly an organic or mineral antigen, such as fungi, thermophilic bacteria, mold, animal proteins (found in bird feathers and droppings), and low molecular weight chemicals (isocyanates).[1]

The incidence of HP varies according to the location studied and geographical and environmental characteristics. The analysis of a large United States healthcare claims database (150 million unique enrollees) showed that the 1-year prevalence rates for HP ranged from 1.67 to 2.71 per 100,000 persons and increased with age to 11.2 per 100,000 in people aged 65 years and older.[2] In Brazil, the occurrence of HP is estimated at 3% to 13% among interstitial lung diseases.[3] To date, few cases have been reported in the pediatric population.

HP has a diverse clinical presentation, including cough, fever, weight loss, dyspnea, respiratory failure, and in more severe cases, pulmonary fibrosis. Several classification schemes have been proposed due to this great variability. One of them classifies the disease into acute (symptoms within hours of exposure), subacute (symptoms within weeks of exposure), and chronic (continued antigen exposure, with no defined frequency).[3]

Corticosteroid therapy for 7 to 14 days with dose tapering may be a useful treatment option. However, the main pillars of HP treatment are environmental control and avoidance of exposure.[4]

Case description

An otherwise healthy 8-year-old boy from a rural area was admitted to a tertiary care hospital with fever, vomiting, dry cough, progressive dyspnea, anorexia, and weight loss for 15 days, with no improvement after two antimicrobial regimens. Physical examination showed tachypnea, moderate respiratory effort, hypoxemia, and crackles at the right base. He was admitted to a pediatric ward for diagnostic workup.

Chest radiograph showed bilateral diffuse micronodular interstitial infiltrate. Computed tomography (CT) of the chest (Figures 1 and 2) showed ground-glass opacities, diffuse involvement, and predominantly centrilobular and acinar distribution, in addition to areas of air trapping at the lung bases, suggestive of HP. Bacterial, viral, and fungal pneumonia, atypical tuberculosis, and bronchiolitis from other causes were ruled out.

In the review of living conditions and habits, the patient's guardian reported the presence of an aviary with about 20 birds in the residence, with which the patient had direct contact by assisting in their care, cleaning, and feeding. Given the epidemiology and imaging suggestive of subacute HP, treatment with methylprednisolone 1 mg/kg/day was initiated and maintained for 7 days.

As a complementary investigation, spirometry for pulmonary function evaluation and bronchoalveolar lavage cellularity analysis were ordered. However, the tests were not performed due to patient limitations.

After corticosteroid therapy and removal of the child from home, he showed complete resolution of symptoms and no longer required oxygen therapy. He was discharged from the hospital with prednisolone 1 mg/kg/day, for later withdrawal. The patient and family members were informed of the importance of avoiding re-exposure to the causative agent to prevent further outbreaks and irreversible lung damage.

Discussion

HP is a diffuse interstitial lung disease of immunoallergic origin caused by repeated exposure to organic or mineral antigens, such as fungi (*Aspergillus*, *Penicillium*, *Micropolyspora faeni*), thermophilic bacteria, mold, animal proteins (present in bird feathers and droppings), and low molecular weight chemicals (isocyanates).[1]

Although the pathogenesis of HP is poorly understood, in genetically predisposed individuals, exposure to these agents is believed to cause sensitization and disease, leading to the production of specific IgG antibodies, with participation of cytokines and interleukins, episodic lung inflammation, formation of immune complexes, and influx of mononuclear cells into the lung parenchyma. This mechanism is also described for delayed hypersensitivity, especially in the subacute form, mediated by CD4 T and T helper lymphocytes.[5]

HP is described mainly in adults because it is often associated with occupational exposure. Although HP can affect people of all ages, it is rare in the pediatric population and probably underdiagnosed, as it is often initially confused with other respiratory tract infections.[6]

There are few data on the prevalence and incidence of HP in children. Studies have estimated the incidence of diffuse interstitial pneumonia in children to be 1.3 to 3.6 cases per million. Among these cases, HP accounts for 2% to 25% of the occurrences.[6,7]

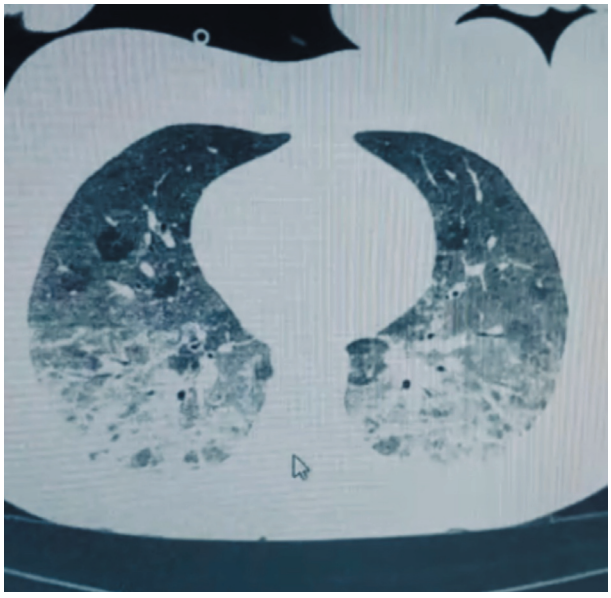

Figure 1
Chest CT scan showing areas of diffuse ground-glass pattern, with small bilateral areas of opacity

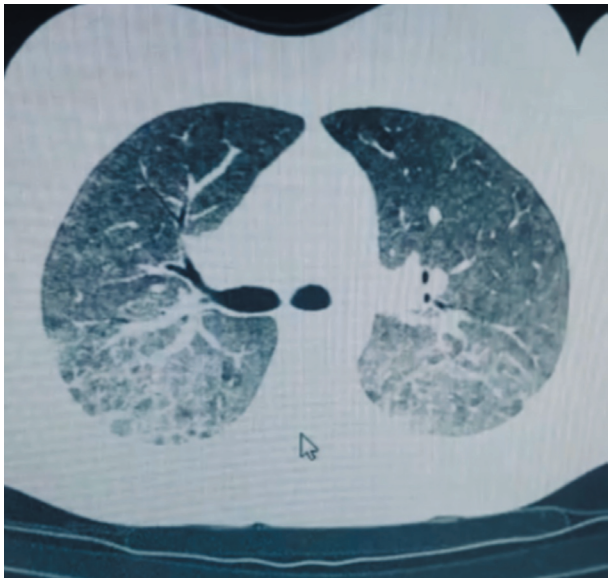

Figure 2
Chest CT scan showing areas of ground-glass pattern and interlobular septal thickening

The clinical presentation of HP in children is similar to that in adults, with dyspnea on exertion and cough as the most common symptoms in children. Weight loss and fever are also frequently found. Physical examination reveals crackles in almost two-thirds of cases.[6]

Several classifications have been proposed because of the variable presentation of HP. Currently, the most widely used one classifies the disease into acute, subacute, and chronic. The acute form presents as a flu-like feverish syndrome, with dry cough and dyspnea, beginning at 4-8 hours after exposure to the antigen. It accounts for approximately 25% of cases and is often confused with viral or bacterial infections,[6] and the symptoms usually improve within a few days. Chest radiograph may reveal a fleeting micronodular pattern in the lower- and mid-lung zones, but patients usually have normal chest radiographs.[8]

The subacute form, as in the present case report, is characterized by gradual development of a productive cough, dyspnea, fatigue, anorexia, and weight loss. Physical examination usually reveals tachypnea and diffuse crackles, and chest radiograph may be normal or show micronodular or reticular opacities that are usually more apparent in the upper- and mid-lung zones.[6,7] In the chronic form, the onset of symptoms is insidious. Digital clubbing may be observed in advanced disease and may help predict clinical deterioration. Disabling and irreversible respiratory findings due to pulmonary fibrosis are characteristic and associated with increased mortality. At this stage, removal of exposure usually results in only partial improvement.[7]

In addition to this classification, a recent clinical practice guideline on the diagnosis of HP in adults recommends the categorization of HP into fibrotic and nonfibrotic according to the presence of radiographic or histological fibrosis. According to the guideline, this classification would better define the clinical course and prognosis of the disease.[9] Although intended for adults, this guideline is the first to provide well-defined criteria for the diagnosis of HP. First, detecting the causative antigen is essential for consideration of HP, workup, and treatment. Serum IgG testing against potential antigens provides no causal relationship and there is no standard hypersensitivity panel; therefore, it has limited applicability. The bronchoalveolar lavage is typically inflammatory, with a predominance of lymphocytes.[9]

As for complementary tests, high-resolution CT of the chest is essential for diagnosis and indicative

of HP when showing at least one of the following findings: ill-defined centrilobular nodules, mosaic attenuation, air trapping, or a three-density pattern (the latter is indicated as highly specific). In their absence, high-resolution CT is indeterminate for HP. Regarding the distribution of lung injury on CT scans, HP is considered typical when it affects the mid-lung zone.[10]

Lung biopsy is not mandatory to establish the diagnosis and may be helpful in doubtful cases. In acute HP, histopathology shows peribronchovascular fibrin deposition and interstitial accumulation of neutrophils, lymphocytes, and macrophages.[11] In subacute HP, there is a classic histological triad of cellular bronchiolitis, predominantly lymphocytic interstitial infiltrate, and interstitial noncaseating granulomas or isolated giant cells. In chronic HP, histopathology shows chronic bronchiolitis, with varying degrees of fibrosis, and peribronchiolar fibroblastic foci.[11,12]

The clinical practice guideline also classifies patients as having definite, high- confidence, moderate-confidence, low-confidence, and not-excluded diagnoses based on information on exposure, CT scans, and bronchoalveolar lavage.[9] Our patient, with a history of exposure to birds, characteristic CT findings, and no bronchoalveolar lavage, had a moderate-confidence diagnosis of HP. In all cases, lung biopsy ensures a definite diagnosis.

Most children are treated with steroids, like our patient. Corticosteroids are widely used for their rapid therapeutic response. However, the identification and removal of the causative agent is paramount for a good response to treatment. Lack of antigen avoidance may lead to disabling and irreversible lung damage in chronic HP.[13]

Corticosteroid therapy approaches include the use of oral steroids and intravenous pulse steroids.[14] There is no consensus on the dosage and duration of treatment, but it should aim at the lowest possible dose and shortest duration. Despite the lack of randomized clinical trials on the topic, the use of immunosuppressive and antifibrotic agents may be considered in adults.[15]

Long-term prognosis depends on factors related to the causative antigen and the patient. Exposure to bird antigens for more than 6 months is associated with residual pulmonary abnormalities. Younger patients are more likely to have a full recovery. Overall, individuals with acute HP show the most marked improvement, with almost complete recovery of lung function. Conversely, those with pulmonary fibrosis have a worse outcome and may progress to respiratory failure, sometimes fatal.[16]

In this context, guidelines on the most appropriate treatment for HP are imperative, especially in the pediatric population for which data are scarce. Moreover, because HP is an uncommon syndrome with a challenging diagnosis, it should always be considered in patients with a positive epidemiological history in order to avoid complications and unfavorable patient outcomes.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Can SARS-CoV-2 trigger a food allergy?

O SARS-CoV-2 poderá ser um trigger para desenvolver uma alergia alimentar?

Inês Falcão[1], Leonor Cunha[1]

ABSTRACT

Due to COVID-19 we are facing unprecedented challenging times in Science, facing the uncertain and the unknown, almost daily facing ourselves with new questions and discoveries. The clinical case described below presents yet another challenge to Science, regarding the interaction between the virus and the immune system. May it be possible that SARS-CoV-2 acts as a trigger factor in a food allergy? The authors report the clinical case of a young man who, upon recovering from COVID-19, developed food allergy to mammalian and poultry meat that he previously tolerated. This pandemic has pushed to the limit the health systems of the entire world, and the fight against it remains far from over. Perhaps only now has it truly begun.

Keywords: COVID-19, SARS-CoV-2, food hypersensitivity.

RESUMO

Os tempos são de pandemia e o percurso da ciência incerto e desconhecido, assim o é desde que apareceu o SARS-CoV-2. O caso clínico a seguir descrito é mais um desafio à Ciência sobre a interação entre o vírus e o sistema imunológico. Será possível que o SARS-CoV-2 seja um fator desencadeante para uma alergia alimentar? Os autores apresentam o caso clínico de um jovem que após recuperar-se da COVID-19 desenvolveu alergia alimentar a carne de mamíferos e aves, que previamente tolerava. Esta pandemia põe à prova diariamente os sistemas de saúde de todo o mundo, e a luta contra este vírus está longe de terminar.

Descritores: COVID-19, SARS-CoV-2, hipersensibilidade alimentar.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted by respiratory droplets, aerosols, and direct contact with fomites. To a considerable degree, the tissue damage in coronavirus disease (COVID-19) is caused by an excessive immune response to infection.[1,2] This occurs due to B and T cells recruitment – exhibiting a predominance of type 1 T helper (Th1) with production of interferon (IFN)-gamma, interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, IL-10, and tumor necrosis factor (TNF)-alpha –, and also the recruitment of neutrophils, monocytes/macrophages, dendritic and endothelial cells, Th1/Th17 lymphocytes, and the production of specific antibodies.[1,2]

Might this intense SARS-CoV-2-infection-provoked inflammatory cascade, known in the scientific community as “cytokine storm”, together with the deregulation of the innate and adaptive immune system, trigger either a food allergy in a patient with pre-existing sensitivity or a new allergy, this is, in a patient without previous sensitivity?

In general, meat allergy is rare when compared to other food allergies and typically happens during childhood, proving scarce in adults.[3] It can be

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separated into two great groups: poultry meat allergy and mammalian meat allergy. Though uncommon, poultry meat allergy assumes a greater frequency than mammalian meat allergy.[5]

Simultaneous allergy to several meats may occur. However, it is more frequent amongst the various types of mammalians or poultry than between mammalians and poultry at the same time.[5] In meat allergy, the immunoglobulin E (IgE)-mediated form proves to be the most common, representing an immediate reaction that usually begins in the first 30 minutes to 2 hours after exposure. Clinical presentation can encompass a wide spectrum, ranging from urticaria, angioedema, and oral allergy syndrome to respiratory, gastrointestinal, and cardiovascular symptoms, in rare cases culminating in anaphylaxis.[5,6]

The pathophysiology of any IgE-mediated mechanism takes place after contact with the implicated antigen and consequent IgE-mediated degranulation of immune effector cells, such as mast cells and basophils, resulting in the rapid manifestation of symptoms. The food allergen-derived epitopes link themselves with IgE molecules bound to the Fc RI receptors on the surface of those effector cells; then the epitope-specific reticulation of IgE-related receptors occurs, leading to the release of pre-formed histamine and other inflammatory mediators of the immediate allergic reaction.[7] Following this early phase reaction, the allergic inflammation is maintained by the production of leukotrienes, activating factor of platelets and cytokines.[7]

Methods

Systematic review of scientific articles found in the data base of National Library of Medicine/ Medical Literature Analysis and Retrieval System Online (PubMed/MEDLINE) and Scientific Electronic Library Online (SciELO) from January 2020 to April 2022. The following medical subject headings (MeSH) terms were used: “Cytokine storm”; “COVID-19”; “food allergy”; “Meat allergy”; “SARS-CoV-2”.

Case report

The authors present the case of a 32-year-old male patient with documented history of allergic rhinitis to house dust mites and storage mites, under prescribed as-needed (p.r.n.) medication as a means to control histaminergic symptoms. The patient denied family history of atopy.

He was referred to the Allergy and Clinical Immunology (ACI) service due to suspicion of food allergy to poultry and mammalian meat.

The patient was infected with SARS-CoV-2 in April 2020 (positive nasopharyngeal swab on 21st April 2020). He reported anosmia, headache, and myalgias that resolved in 3 weeks using only symptomatic medication (paracetamol), with documented cure on 15th May 2020 (nasopharyngeal swab). He denied respiratory, gastrointestinal, cardiovascular, or other neurologic symptoms.

Three weeks after the cure he began experiencing episodes of general discomfort, abdominal colic, and too-soft, sometimes liquid feces after ingesting chicken, turkey, pork, and rabbit. He immediately opted for an eviction diet for the mentioned meats and was directed to the ACI service of Centro Hospitalar e Universitário do Porto by his assistant physician. He denied complaints associated with the ingestion of beef. Previously, he ingested all types of mammalian and poultry meat without any symptoms.

He had no recent history of insect bites, namely tick bites, as well as no history of recent outdoor activities.

From the consequent study emphasis must be placed on the skin prick tests conducted with Leti® commercial allergen extract (mm): (histamine 10), chicken meat 8, rabbit meat 7, beef meat negative, and pork meat 6. Skin prick tests for aeroallergens were also run, appearing positive for *Dermatophagoides teronyssinus* 13, *Dermatophagoides farinea* 8, *Lepidoglyphus destructor* 9, and dog 7. From the analytic study it is important to highlight the following: total IgE of 195 KU/L, beef meat 0.02 kUA/L, pork meat 1.21 kUA/L, chicken meat 2. 03 kUA/L, turkey meat 0. 97 kUA/L, and alpha -gal 0.01 kUA/L.

The performed hemogram showed no significant alterations. Both the kidney function test and the ionogram also displayed measurements within the reference values.

Oral food challenge was performed, and 20 minutes after ingesting approximately 15 mg of cooked chicken meat, the patient developed facial erythema and pruritus, eyelid angioedema, followed by diffuse abdominal pain. Similar signs and symptoms were documented after the ingestion of 20 mg of cooked pork meat. As the patient did not like eating rabbit meat, he refused to perform the oral food challenge.

Conclusion

The temporal frame reported by the patient is unequivocal, and food allergy to mammalian and poultry meat has been confirmed. Nonetheless, the immunologic mechanisms for this allergy potentially triggered by SARS-CoV-2 require further investigation.

This case report aims to alert allergists and immunologists as well as professionals from other medical fields to the possibility of encountering an increasing number of patients with symptoms consistent with food allergy after infection with SARS-CoV-2. It hopes to prevent such cases from being disregarded, so that we may understand the true extent of COVID-19 impact on our immune system.

The way this virus triggered a food allergy remains a hypothesis. Did it happen due to the "cytokine storm" or "a cross-reactivity mechanism"? The answer is imperative, as is the ability to control this pandemic, which surprises us daily with new sequelae. It is most likely that the patient was already sensitized to the referred meats and that COVID-19 acted as a trigger to develop allergy (becoming symptomatic) by dysregulating the immune system,

The patient keeps the eviction diet for chicken, turkey, pork, and rabbit meats, and also for egg. He has p.r.n. medication for accidental exposure, namely antihistamine and corticosteroid. He is still being followed in the ACI service for medical surveillance.

Apart from the hypothesis that SARS-CoV-2 triggered this allergy, the case proves outstandingly peculiar, because the patient exhibits a simultaneous allergy to poultry and mammalian meat.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Environmental pollution, public health, and energy sources

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Dear Editor,

The concern about the issue of energy sources and environmental impact has been the subject of large studies. This issue has not proved to be an easy equation, as it must consider several aspects with great impact on mankind, such as health, economic, social, and cultural factors, among others.

The replacement of fossil energy sources with low-carbon emitting technologies has been the focus of studies and discussions, with the establishment of goals and efforts at a global level.[1-3] Several energy sources were shown to be efficient, such as wind, solar, biomass, and hydroelectric energy, among others.[4] The process of replacing energy sources has already begun with progressively discontinuing of fossil fuels, although the speed with which these established goals will be achieved remains unknown.

The major impacts of climate change and environmental pollution on health are of great concern.[5-11] Pollution has been identified as one of the main risk factors for global morbidity and mortality,[7] responsible for the increased incidence and mortality of cardiovascular, respiratory, neoplastic, metabolic, and genetic diseases.[5-7,9]

Environmental pollution consists of particulate matter of different sizes and chemical compositions, grouped into three different categories according to particle size: PM10, PM2.5, and ultrafine particles. It is formed by different chemical compounds, including sulfur dioxide (SO_2), ozone (O_3), nitrogen oxides (NO_2, NO), and carbon dioxide (CO_2).[7,10] Once inhaled, the particulate material, especially PM2.5 and ultrafine particles, reaches the lungs and is capable of reaching smaller bronchi, bronchioles, and alveoli, causing an inflammatory reaction and producing carcinogenic substances in the mucosa of the respiratory tract.[12] The particles may also enter the bloodstream and cause cardiovascular problems, oxidative stress, and several other diseases through various pro-inflammatory mechanisms.[12]

Some diseases have been particularly affected by the increase in environmental pollution, both regarding worsening of symptoms and increase in mortality, such as chronic obstructive pulmonary disease (COPD), ischemic heart disease, stroke, respiratory infections, lung cancer, diabetes, cataracts, and asthma.[6,7,9,11,13]

Health-related costs are estimated to be very impactful. Studies have shown a significant increase in hospital visits, including visits to the emergency room due to respiratory problems and asthma exacerbation, in periods of higher concentrations of particulate matter in the atmosphere.[5,10,11,13]

There is evidence of a synergistic effect between temperature and pollution, with temperature worsening the deleterious effects of pollution on health. In this sense, worsening of respiratory symptoms was associated with increased pollution and high temperatures, whereas higher incidences of cardiovascular problems were associated with increased pollution and low temperatures.[14]

Fossil fuel burning from vehicles and industrial processes is the main cause of pollution in urban centers.[15] Particulate matter emission resulting from fuel burning by urban vehicles is estimated to account for 37% of urban pollution rates (CETESB, 2018).

Another study showed that the use of ethanol can reduce CO_2 emission by up to 80% compared with gasoline.[2]

Specifically related to the relationship between pollution and health, some more prevalent diseases are worthy of note due to the proportion of their socioeconomic consequences. Asthma, for example, is the most prevalent chronic respiratory disease in the world, affecting 358 million people.[5]

Researchers found that increased concentrations of particulate matter were associated with an increase in patient visits to emergency services and hospitalizations due to asthma exacerbation.[5,10,16] Increased pollution was also associated with an increase in medical appointments due to cardiovascular diseases such as angina, myocardial infarction, and stroke.[6,8] Prolonged exposure to environmental pollution also negatively affects other diseases, such as rhinitis, hypertension, neurodegenerative disorders, premature skin aging, premature birth, low birthweight, and fertility problems.[7]

Recent studies reported that pollution not only directly affects health, but also the economic sector due to increased demand in the health care system, medical appointments, additional tests, hospitalizations, and medications. Increased absenteeism and decreased work productivity and school performance also play a significant role.

Some populations are known to be more vulnerable to the deleterious effects of pollution exposure, such as people with pre-existing conditions (asthma, allergic rhinitis, COPD, pulmonary fibrosis, hypertension, arrhythmias, ischemic heart disease, diabetes, obesity), children < 5 years old, older adults > 80 years old, taxi drivers, pregnant women, people with genetic susceptibility, populations living close to industrial centers with little access to healthy food, and residents of large urban centers who use public transport in locations with heavy traffic.[7] These populations require greater attention in situations of critical pollution levels.

Considering the aforementioned, the search for alternative energy sources that emit less particulate matter is clearly crucial. Biofuels have proved to be a viable alternative. Brazil has a privileged position in this issue because of climatic conditions and territorial extension. The development of new technologies allowed the use of ethanol, which reduced CO_2 emissions by up to 80%.[2,4]

Biodiesel should also be carefully considered due to its capacity to reduce pollutant emission when used in urban transportation.[4] Mixing biodiesel with diesel is already a reality, with a proven reduction in the emission of particulate matter.[4]

The research and development of low-carbon emitting technologies have positively contributed to the fight against environmental pollution. It should be noted that we are facing something new, and careful observation of what may come from these changes is still necessary.

Field management in monocultures of sugarcane, for example, which is used to obtain biofuels, can have major impacts on the soil and the environment.[17] The legislative branch needs to urgently look at this new reality with care and responsibility.

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