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Review

Non-steroidal antinflammatory drugs as cofactors in hypersensitivity diseases

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ABSTRACT

Althoug many hypersensitivity diseases have been extensively investigated, little information is available in the literature about possible cofactors contributing to those reactions and the comorbidities that should be taken into account when assessing a patient complaining of adverse reactions triggered by exposure to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs can be cofactors for many clinically relevant conditions, especially food-dependent exercise-induced anaphylaxis, chronic urticaria, uncontrolled asthma, angioedema induced by angiotensin-converting enzyme inhibitors, and oral mite anaphylaxis. Although the role of NSAID use as cofactors has not been fully evaluated in children and adolescents, awareness on these relationships is required for the correct diagnosis, classification, and treatment of affected patients.

KEYWORDS: cofactors in hypersensitivity diseases, anaphylaxis, chronic urticaria, angioedema

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INTRODUCTION

Cofactors are external or patient-related circumstances that can produce or aggravate allergic diseases. There are many cofactors and their mechanism of action is not yet clearly known. The most important cofactors in children and adolescents are physical exercise and concomitant infections, while in adults drugs and alcohol are also often involved. Other factors have been reported such as stress, menstruation, unfavorable weather conditions, and sleep deprivation. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs in children [1] and, according to a ENDA/EAACI position paper [2], they are, after antibiotics, the second cause of drug hypersensitivity reactions in children. A 19.6% positivity rate was reported using a drug provocation test (DPT) [3], with paracetamol and ibuprofen the most common culprit drugs. Reactions to NSAIDs in children are usually favored by concurrent infections or concomitant physical activity and are related to a non-immunological response. In this paper we will examine diseases in which the use of NSAIDs as cofactors is more frequent. NSAIDs can elicit a preexisting condition and/or worsen a disease.

ASTHMA

Asthma is a major non-communicable disease, affecting both children and adults.

The prevalence of the disease in recent decades has increased worldwide, especially among children. The reasons for increasing prevalence in children are unclear, but is likely due a to complex interaction of several risk factors.

Frequent and early use of pharmacological agents, such as analgesics and antipyretics, may be a cofactor in the pathogenesis of childhood asthma. The use of aspirin in children should be avoided when possible, because of concerns about a causal relationship between aspirin and Reye's syndrome [4] and "aspirin exacerbate respiratory disease (AERD)", characterized by asthma, chronic rhinosinusitis with nasal polyposis [5] that may affect children**.**

As a result, ibuprofen and paracetamol have become the most widely used medications to control fever and pain in children. The predisposing role of paracetamol and ibuprofen for the development or exacerbation of wheezing and asthma among children remains uncertain [6-8].Inhibition of cyclooxygenase (COX) by ibuprofen can lead to activation of the lipoxygenase system, resulting in increased leukotriene synthesis, and subsequent bronchospasms and asthma exacerbation. Unlike NSAIDs, which inhibit COX-1 and COX-2 enzymes throughout the body, paracetamol mainly acts by inhibits prostaglandin synthesis in the central nervous system. Therefore, it is not considered an anti-inflammatory drug.

Although no explicit warning has been issued for paracetamol, in recent years several studies have highlighted the risk of asthma exacerbations associated with this drug, particularly in children [9]. Paracetamol may be linked to impaired lung function and asthma primarily through oxidative stress due to reduced glutathione concentrations in the lungs. Bronchospasm due to leukotriene release may be triggered by reactive oxygen species in asthmatic patients [10,11]. Based on these potential effects, several studies have been conducted to establish whether the use of paracetamol or ibuprofen is associated with the occurrence of bronchospasm or asthma exacerbation. The number of placebo-controlled studies in children with fever and pain is limited, making it difficult to compare the risk of asthma exacerbation between children who do and do not use antipyretics [12,13]. It is of interest that a meta-analysis of randomized controlled trials showed no difference between paracetamol and ibuprofen in the risk of asthma exacerbation in children [10]. A recent systematic review compared the effects of ibuprofen, other antipyretics and analgesics, and placebo in the general population and in asthmatic children. The meta-analysis of data from a few randomized controlled trials and several observational studies found that ibuprofen may provide protection against asthma-like symptoms in the general population when used to relieve fever or bronchiolitis. In contrast, it may cause asthma exacerbation in subjects with pre-existing asthma. Comparing ibuprofen with paracetamol or other NSAIDs, no evidence of an increased risk associated with ibuprofen was found in either the general or asthmatic population [14].The answer to the important practical question of which drug to use when asthmatic children have fever or pain requiring treatment is that there are no significant differences in asthma exacerbations when using ibuprofen or paracetamol.

Although AERD appears to be rare in children, based on the assumption of significant cross-reactivity between aspirin and other NSAID, a history of severe asthma exacerbation after NSAIDs administration can suggest NSAID-exacerbated respiratory disease (NERD) [7, 14]. Finally, it is worth noting that respiratory infections are the main trigger of asthma exacerbations in children and this represents a confounding factor in studies on the effects of antipyretics in asthmatic children [15].Since research in this area is limited and based primarily on observational evidence, high-quality trials are needed to clearly define asthma outcomes after ibuprofen or paracetamol administration, across different clinical settings, at varying doses, and with longer follow-up.

CHRONIC URTICARIA

Chronic urticaria (CU), defined by the persistence or recurrence of wheals, angioedema, or both for more than 6 weeks, is an uncommon but significant burden in the pediatric setting, often causing recurrent visits due to children's discomfort and parents' concern. Prevalence, clinical pictures, underlying causes and therapeutic response seem to be comparable to those observed in adults [16], with a point prevalence of 1.43%, with no sex difference under 15 years of age [17]. The most frequent type is chronic spontaneous urticaria (CSU) whose pathogenic mechanisms are still not completely clear (autoimmune or autoallergic) and, by definition, without an identifiable trigger [18]. Balp et al. observed, in a study involving children in 5 European countries, a one-year diagnosed prevalence of 1.38% for CU and 0.75% for CSU. NSAIDs are a known specific cause of immediate skin hypersensitivity reactions [19]. NSAIDs can elicit IgE-mediated reactions such as in single-NSAID-induced urticaria/angioedema/anaphylaxis (SNIUAA). They can also trigger skin reactions by COX-1 inhibition with cross reactivity [20] among NSAIDs belonging to different classes. They include NIUAA and NSAIDs-exacerbated cutaneous disease (NECD), causing urticaria and/or angioedema in patients with CSU. NSAIDs are the most common type of drug eliciting CU and CSU exacerbations [21]. In a group of 423 patients (52 children, 2-18 years old) [22] NSAIDs were reported by patients as the first cause of CU (4.2%) and CSU (16.6%) exacerbation. Sanchez et al. [23] evaluated 245 patients (mainly adults) with CSU, reporting that 41.1% had a positive DPT in patients with CSU compared to none in controls. Cavkaytar et al. [24] confirmed a positive aspirin DPT in 24% of children and 10% of adolescents with CSU and recurrent urticaria, respectively. Sanchez-Borges et al. [25] have also documented a distinct sub-phenotype of CSU caused by aspirin observed in some pediatric children.

The relationship between NIUAA and CSU is still under debate, since some studies demonstrate a non-evolutionary relationship [26] while previous studies suggested otherwise [27].The exacerbations of CSU after NSAIDs intake are determined by a non-immunological mechanism due to the inhibition of COX-1. A decrease in prostaglandin

E2 (PGE2) synthesis and an increase in cysteinyl leukotriene (LTC4-D4-E4) production are responsible for mast cell activation and degranulation [28]. Other mechanisms probably involve eosinophils and platelets mediators, PGD2 and its metabolite 9α,11β-PGF2, and some immune system mediators such as IL-33 and TSLP [29].

Most published studies investigating the relationship between CU and NSAIDs relied only on clinical history that must be always carefully collected. Unfortunately, regarding NSAID hypersensitivity in CSU, the pathogenic mechanism is not immune-mediated. Therefore, skin tests are not useful for diagnosis and a DPT in a safe and equipped environment is commonly needed. A few in vitro tests are available but are usually restricted to research settings and have not been fully validated in pediatric age [29]. At present, there is no worldwide consensus with regard to a specific DPT protocol in children [3]. It has been suggested to avoid a DPT with aspirin in patients with NECD and active CSU or recurrent urticaria since these patients usually react to NSAIDs at any dose [21].

Most recent guidelines specifically advise to avoid NSAIDs in CU, unless essential [17,30]. In case of a positive DPT to a COX-1 NSAID, it is imperative to provide the patient with a safe alternative, organizing a DPT with lower dose of a strong COX-1 inhibitor, a full-dose with a weak COX-1 inhibitor, or a selective COX-2 inhibitor [31], which are usually considered safe in pediatric age, although with age-related limitations [32]. It has also been demonstrated that in many cases, premedication with antihistamine allows the patient to tolerate the drug without reactions [33].

FOOD ALLERGY

It has been demonstrated that NSAIDs are able to trigger or exacerbate allergic reactions to food allergens. This phenomenon occurs when NSAIDs are taken within approximately 4 hours (either before or after) the ingestion of the culprit food [34]. These reactions are often misdiagnosed as hypersensitivity reactions to NSAIDs. Two types of reactions may occur [21]:

- NSAID-exacerbated food allergy (NEFA): the occurrence of a severe allergic reaction when NSAIDs are taken in close temporal proximity to food allergens that would normally cause only mild symptoms, such as oral allergy syndrome.
- NSAID-induced food allergy (NIFA): the occurrence of an allergic reaction when NSAIDs are taken in close temporal proximity to food allergens that are usually tolerated without causing any symptoms.

It has been shown that approximately 18% of suspected allergic reactions to NSAIDs in adults actually belong to one of these two categories. NSAID appear to increase gastrointestinal barrier permeability by reducing prostaglandin production. As a consequence, food allergens are more likely to cross the epithelial barrier and trigger an allergic reaction [1]. A similar mechanism of action has been described for physical exercise and alcohol consumption, both of which may likewise exacerbate or trigger food-related allergic reactions. The allergens most commonly involved in this mechanism are ω-5 gliadin (Tri a 19) and lipid transfer proteins (LTP), particularly peach (Pru p 3) [35-38]. The central role of LTP may be explained by the fact that they are ubiquitous in the plant kingdom and share structural homology with proteins from many other plant species. These sensitizations are highly prevalent in the Mediterranean area.

Sánchez-López et al. conducted a study demonstrating that reactions commonly linked to NSAIDs are actually classified as either NIFA or NEFA. In their cohort, 16% of adults initially suspected of having NSAID hypersensitivity were ultimately diagnosed with NIFA/NEFA. Among these patients, 84.6% were sensitized to lipid LTPs, predominantly Pru p 3, while 11% were sensitized to gliadin [36]. Similarly, Romano et al. investigated NEFA/NIFA and identified Pru p 3 as the main allergen involved in these reactions [34]. More recently, Ruano-Zaragoza et al., in a study including 528 adults sensitized to Pru p 3, reported that more than 30% experienced cofactor-related allergic reactions, frequently triggered by NSAIDs [35]. However, it should be emphasized that the incidence of Pru p 3 sensitization varies considerably according to geographic area; for instance, it is very uncommon in the United States.

Of note, some cofactors can be necessary in NEFA/NIFA. Food-dependent exercise-induced anaphylaxis (FDEIA) is characterized by tolerance to food or exercise alone, and occurrence of anaphylaxis when a specific food is ingested 4-6 hours before physical exercise (sFDEIA). In some patients, a non-specific meal before exercise predisposes to the development of anaphylaxis (nsFDEIA). In wheat-dependent exercise-induced anaphylaxis, ASA reduces the threshold and increases the severity of the allergic reaction [39]. In some cases of NIFA, anaphylaxis occurs only if an NSAID, especially aspirin, and food are taken before exercise [39].

In some cases, anaphylaxis can be triggered by the combination of 4 factors, cow's milk, exercise, aspirin or ibuprofen, and menstruation [40].

The diagnosis is based on clinical suspicion, which arises when patients report the onset of immediate cutaneous and/or anaphylactic reactions following NSAID intake. In such cases, a detailed clinical history should be obtained to assess whether food ingestion occurred in association with NSAID intake, which foods were consumed, and the time interval between food ingestion and NSAID administration. If the clinical history is positive for ingestion of a food allergen within 4 hours before or after NSAID intake, skin prick testing for major food allergens and measurement of serum specific IgE levels for food extracts and molecules should be performed. If sensitization to a specific food is identified, a drug challenge with the suspected NSAID should be carried out, ensuring that the foods testing positive are avoided for at least 4 hours before and after the DPT [21]. If the patient passed the NSAID provocation test, a diagnosis of NEFA or NIFA can be made with a high degree of probability. In these patients, it is not necessary to discontinue either the consumption of foods to which sensitization has been demonstrated or the use of NSAIDs. The only recommendation is to avoid NSAID intake within 4 hours before and after consuming a meal containing foods that tested positive in the allergological workup [21]. Prevention of NSAID dependent FDEIA requires exercising with a person who can help if a reaction occurs,

avoiding the involved cofactors, food and NSAID, for at least 4 hours before exercise, and carrying autoinjectable adrenaline.

ANGIOEDEMA

Angioedema (AE) is a recognized adverse drug reaction of medications that act on the renin-angiotensin system, in particular the angiotensin-converting enzyme inhibitors (ACEi). ACEi therapy is one of the most relevant causes of drug-related induced angioedema (ACEi-AE) and a relatively large number of cases occur because of the widespread use of this drug class in antihypertensive therapy. The incidence of AE-ACEI is thought to be 0.1-0.7%, but in some studies the reported rate is as high as 2.2 to 6% [41]. Approximately one-third of all angioedema cases admitted to the emergency department are caused by an ACEi [42]. However, this disease is very rare in pediatric age. The clinical presentation of ACEi-AE is usually mild; however, fatalities secondary to angioedema of the upper airways and subsequent airway obstruction have been reported [43]. Despite that an increase in the level of bradykinin – a consequence of ACEi therapy – is implicated as a key factor in the development of ACEi-AE, the pathophysiological mechanism remains unclear, and individual ACEi-AE susceptibility is assumed to be dependent on genetic predisposition and contributing or interacting environmental factors as smoking, seasonal allergies, antihistamine use, corticosteroid use, and certain foods [44]. In addition, some traumatic situations (facial impairment, anesthesia, intubation, transplantation, cardiac catheterization) have been incriminated in the occurrence of these AEs. In some reports diabetes seems to be protective for ACEi-AE development [45].

The concurrent use of NSAIDs and ACEi can trigger, precipitate, or worsen AEs in patients already taking ACE inhibitors. Combination of aspirin or NSAIDs with ACEi cause about 50% of all AE cases related to ACEi [46]. This interaction is very dangerous because it combined two different types of medications known to cause AE and may cause a severe disease and life-threatening reactions due to upper airway obstruction. Other medications (immunosuppressive drugs, lidocaine) have also been described as potential triggers [47].

In addition to angioedema the combination of an ACEi, a diuretic, and an NSAID or metamizole (combination known as "triple whammy") significantly increases the risk of acute prerenal kidney injury (AKI) [48-49]. Inhibition of the renin-angiotensin-aldosterone system (RAAS), enhances the role of prostaglandins in the regulation and maintenance of hemodynamic glomerular function. The synthesis of prostaglandins is inhibited by NSAIDs. Although it does not represent a hypersensitivity disease, it is important to know the risk associated with the combination of these 3 drugs.

Pancake Syndrome

Oral Mite Anaphylaxis (OMA, also called pancake syndrome or pancake anaphylaxis) is a newly recognized clinical syndrome characterized by severe, potentially life-threatening, allergic symptoms occurring in allergic individuals after exposure through the oral route to foods containing mites, mainly flour. Foods at risk are pancakes, beignets, cheese, ham, chorizo, and salami. Optimal conditions for mite growth are needed, as longer storage times have been associated with increased frequency of OMA (temperature >27°C, humidity >70%). OMA is observed more frequently in tropical countries, but also in northern countries [50].

Most patients are adolescents and young adults, and there is no sex predominance. All have a previous history of atopic disease, more often rhinitis, asthma, or both. Symptoms typically begin within the first 10 to 45 minutes after the meal. Outstanding symptoms are dyspnea, face and laryngeal angioedema, wheezing, and other upper and lower airway manifestations [51].

The association of OMA with exercise-induced anaphylaxis cases has been reported by two groups of investigators, and this clinical pattern has been designated as dust mite ingestion-associated exercise induced anaphylaxis [52]. Mites responsible for OMA include domestic species (*Dermatophagoides pteronyssinus*, *D. farinae*, and *Blomia tropicalis*), as well as storage mites (*S. medanensis, Aleuroglyphus ovatus, Lepidoglyphus destructor, Tyrophagus putrescientiae, Tyreophagus entomophagus*, and *Blomia freemani*).

Diagnosis of OMA is based on the following findings [53]: 1) Acute respiratory symptoms temporarily associated with the ingestion of food made with flour; 2) Mite sensitization demonstrated by positive prick tests to mite extracts; 3) Negative skin test with commercial wheat extract; 4) Positive prick test to the incriminated flour; 5) Microscopic identification of mites in the flour.

An increased prevalence of NSAIDs cutaneous hypersensitivity (i.e. urticaria and angioedema) has been reported in patients with OMA. Because of this association, ''a new aspirin triad'' was proposed [54]. This potential clinical triad is characterized by allergic rhinitis, aspirin hypersensitivity, and severe reactions to the ingestion of mite-contaminated foods. The reasons for this association have not been elucidated because mite-induced anaphylaxis is mediated by mite-specific IgE, whereas most reactions to NSAIDs occur in patients by inhibition of COX-1 and are not dependent on IgE [52]. A possible mechanism that might explain this association includes inhibition of COX-1 by mite constituents. Predisposing factors may be genetic (such as polymorphisms of leukotriene C4 synthase), stimulation of innate immunity by mite products; protease activity; Toll-like receptor 4-mediated inflammation; and epigenetic modifications [55].

Exercise-Induced Anaphylaxis

Drug-dependent Exercise-Induced Anaphylaxis is a rare condition that occur when a specific drug is ingested before physical exertion. ASA is most commonly culprit, but different NSAIDs such as naproxen have been described [56].

CONCLUSIONS

The phenomenon of cofactors is well known but frequently neglected. Along with identifying the eliciting allergen, routine assessments of the possible involvement of cofactors are essential for the management of patients with many hypersensitivity diseases. In patients with a

suggestive history of a disease where cofactors may be involved, the diagnostic allergic work up should be modified. For example, oral food challenges combined with a suspected cofactor should be performed. Most mechanisms of action of cofactors have limited evidence, and further studies are urgently needed. This knowledge will help to design both tailored treatments and prophylactic strategies.

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