



Figura 1:

Pacientes con sospecha de enfermedad respiratoria exacerbada por la aspirina.

Patients with suspected aspirin-exacerbated respiratory disease.

4. El personal de salud también tiene como responsabilidad educar al paciente en el conocimiento de su enfermedad y el uso racional tanto de medicamentos (AINES) como alimentos o productos naturistas que contengan salicilatos.

allergies, with special attention in asthmatic patients, as asthma may trigger allergic reactions to our conventional analgesic management secondary to dental treatment.

Keywords: Aspirin exacerbated respiratory disease, aspirin desensitization, chronic sinusitis, asthma, nasal polyps, Samter's triad.

Literature review

Aspirin exacerbated respiratory disease (AERD), a disease little known to the dentist. Study guide and management

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ABSTRACT

Aspirin-exacerbated respiratory disease (AERD) is chiefly characterized by the following symptoms: nasal polyps, chronic sinusitis, asthma, and sensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the enzyme cyclooxygenase-1 (COX-1). Ingestion of aspirin and most NSAIDs may result in a spectrum of allergic reactions manifested mainly in the upper and/or lower airways. The allergic reaction can become severely complicated and produce laryngospasm and/or bronchospasm. **Objective:** To create a simple study guide to alert the general dentist in the analgesic management of patients with AERD. **Conclusion:** AERD is a chronic, underdiagnosed disease that requires performing a patient's careful medical history and interrogation of prior history of both pharmacological and food

BACKGROUND

Aspirin-exacerbated respiratory disease (AERD) is a complex syndrome consisting of chronic inflammation of the respiratory mucosa in which patients experience symptoms of bronchial asthma, nasal polyposis, chronic rhinosinusitis, and sensitivity to aspirin as well as other non-selective inhibitors of the enzyme cyclooxygenase-1 (COX-1).¹⁻³ AERD is part of the broad spectrum of hypersensitivity reactions induced by nonsteroidal anti-inflammatory drugs (NSAIDs), such as urticaria-angioedema exacerbated or induced by multiple NSAIDs, anaphylaxis induced by a single NSAID, or late reactions secondary to NSAIDs.^{2,4}

This condition is also known as Samter's Triad or Samter's syndrome (asthma, nasal polyposis and aspirin/NSAID intolerance).^{5,6} The first to describe various cases of severe asthma attacks after aspirin ingestion was Felix Hoffmann, shortly after the discovery of aspirin in 1897.⁷

In 1922, Widal et al. were the first to describe the association between nasal polyposis, bronchial asthma, and aspirin intolerance.⁵ In 1967, Samter and Beers defined the triad of aspirin or Samter's triad, as we know it today.^{3,6}

MATERIAL AND METHODS

Design: systematic reviews of the literature and description of clinical cases and their follow-up of patients with respiratory disease exacerbated by aspirin and/or Samter's syndrome were consulted.

Search strategy. A search on aspirin allergy and Samter's syndrome was conducted in internationally published articles and clinical practice guides. The search for systematic reviews of scientific literature was carried out at the PubMed Library, Science Direct, and Scielo in both Spanish and English with the following keywords: aspirin exacerbated respiratory disease, aspirin desensitization, chronic sinusitis, asthma, nasal polyps, and Samter's triad. No date limit was established. Update and review articles were chosen. The search was complemented with the analysis of bibliographic references from the articles selected for the review.

Inclusion and exclusion criteria: In the search for literature, those articles who made an updated review of the literature on AERD and Samter's syndrome were selected. In addition, a search for recommendations on alternative drugs for use in aspirin-allergic patients was done.

Data extraction. After the initial search, 1,621 articles were found in English and four articles in Spanish with the keywords used. Those that were not reviews of the literature or updates of the disease were excluded. Abstracts were reviewed and those whose full text was available were chosen through the Metropolitan Autonomous University website (<https://www.xoc.uam.mx/>).

Data analysis. The information obtained was analyzed to be structured in simple and concrete sections on disease definition, epidemiology, pathophysiology, etiology, clinical picture, and treatment. No clinical practice management guides were found about this specific disease, so we decided to make an approach with the recommendations presented in this article.

RESULTS

Epidemiology

The prevalence of the aspirin triad, i.e. aspirin intolerance (AI), bronchial asthma (BA), and nasal polyposis (NP) in the general population ranges from 2% up to 12.4%, according to some authors. In adult patients diagnosed with asthma the prevalence increases to 7.5% and in severe asthma to 14.8%.^{5,8}

Of the patients with AI, 78% have the triad. Between 48 and 95% of patients with aspirin-induced asthma

(AIA) have NP, and up to 70.8% of patients with NP have AI and BA.

The prevalence of AERD is greater in women with a 2.5:1 ratio. They also present the most severe complications. The disease is more common between the ages of 30 and 40 years.^{1,6,8}

Etiopathogenesis

- AERD is a form of atopic disease with genetic predisposition.^{3,9}
- High levels of total immunoglobulin E (IgE) and histamine may be found depending on whether it is the second or first exposure to the drug, respectively.^{5,10}
- NSAID use in these patients triggers respiratory allergic symptoms minutes after administration of the medicine.^{3,9}

Pathophysiology

The physiological mechanisms and respiratory symptoms associated with AERD are not fully understood. The most accepted hypothesis is based on changes in arachidonic acid (AA) metabolism with abnormal overproduction of cysteinyl leukotrienes (CysLTs) and pro-inflammatory prostaglandins (PGs).^{2,11}

AA is an essential fatty acid present in the phospholipids of the metabolized cell membrane of cyclooxygenase (COX) and the lipoxygenase pathway (LOX), which generate different eicosanoids (prostaglandins, leukotrienes, thromboxanes, etc.) responsible for triggering symptoms.⁵

According to one theory regarding the alteration of AA metabolism in patients with AERD, aspirin and other NSAIDs would inhibit the COX-1 enzyme, diverting the AA metabolism toward the LOX pathway, thus promoting increased Cys-L levels.^{2,6} These reactions are accompanied by idiosyncratic activation of mast cells, marked eosinophilic inflammation of the respiratory tract, and an increase in leukocytes attached to platelets.^{10,11}

Activation of basophils, eosinophils, macrophages, mast cells, platelets, lymphocytes, and eicosanoid molecules trigger an increase in vascular permeability, plasma exudation, and edema, which are related directly to the main symptoms of AERD, such as mucus hyperproduction and bronchoconstriction.^{5,11,12}

Clinical picture

The clinical picture can start between the third and fourth decade of life, with persistent rhinitis usually related to anosmia, which progresses to persistent

pansinusitis that can become severe. Two years after rhinitis has started nasal polyps appear. Also, asthma can develop within three to five years after onset of rhinitis (*Table 1*).^{1,3-5}

Allergic reactions to aspirin can occur throughout the course of the disease; they usually appear at a dose of 40-160 mg (enough to block COX-1 but not COX-2) with symptoms usually limited to the respiratory tract.^{4,11,13}

Patients with AERD will develop upper and lower airway symptoms within 30 minutes and up to 3 hours after intake of the medication.^{3,5,6}

An association between alcohol consumption and AERD has been reported. In one study, 83% of patients showed upper or lower airway respiratory symptoms associated with alcohol consumption.⁴

Diagnosis

Presence of asthma, rash, nasal drip, nasal polyposis, hyposmia or anosmia, sometimes gastrointestinal symptoms, and even cardiovascular symptoms in response to a hypersensitivity reaction after NSAID intake is very likely to be an AERD.^{14,15}

The influence of genetic background should also be considered.^{3,5} There are currently no specific laboratory tests for diagnostic confirmation, so upon clinical suspicion, the patient should be referred to an allergy expert. The specialist can make the accurate diagnosis of this disease by subjecting the patient to provocative tests with established protocols for aspirin or other NSAIDs, which consist of administering increasing doses and evaluating the presence of symptoms in relation to the intake of the drug.^{13,16}

As for laboratory studies, although they may be nonspecific, a marked serum eosinophilia and increase in leukotriene E4 may be found in urine.^{11,14}

Nasal discharge cytology and polyp histology reveal abundant eosinophilic infiltration.^{11,17}

The specialist will complement the study with fibronasolaryngoscopy and CT scan to confirm nasal polyps.^{5,9,17}

Treatment

The treatment of AERD consists of the medical management of asthma, chronic rhinosinusitis, pharmacological and/or surgical treatment of nasal polyps, the use of leukotriene and corticosteroid antagonists, as well as the avoidance of NSAIDs/aspirin use.^{2,17}

For the specific treatment of allergies to salicylates inactivation or desensitization is indicated. The

procedure starts by performing a provocation test. Just after the test the dose immediately below the reaction dose can be used as a starting dose to desensitize; this is done by protocols using ascending doses.^{2,16} Depending on the procedure and patient tolerance, this can last from few days to two weeks.

In approximately 80% of cases, improvement is reported with the desensitization treatment. Better nasal breathing and sense of smell and absence of recurrent polyps is observed. This recovery is maintained within two to three years.^{3-6,11}

Prevention and safety of intake of ther NSAIDs

Patients with AERD have increased morbidity, characterized by more emergency hospital care when compared with asthmatic patients not allergic to aspirin. Identification of this syndrome is critical because asthma exacerbations secondary to aspirin sensitivity have significant morbidity and can be tragic and/or costly.⁸

Some publications indicate that patients reacting to aspirin also react to several NSAIDs that inhibit COX-1, so NSAIDs are contraindicated in patients with the triad.^{5,6} The results of the study published by Járes et al. are alarming. They observed that in Latin America NSAIDs, with around 52% of use, are the leading cause of adverse effects that can produce non-predictable reactions; those effects are rarely dose-dependent, have low morbidity but high mortality, and respond to the withdrawal of the drug.^{3,18}

Paracetamol is recommended at doses less than 1,000 mg, as it is a partial COX-1 inhibitor. Partial COX-2 inhibitors and selective COX-2 inhibitors are also recommended (*Table 2*).^{3,19}

Low doses of opioids such as buprenorphine or tramadol may be used.^{1,7,15}

It cannot be overlooked that coxibs have been associated with severe cardiovascular effects, such as acute myocardial infarction, which is the reason that their indication in patients with cardiovascular risk factors should be performed very carefully. Adverse reactions of opioids should also be taken into account. *Table 2* displays the names of medications that must be avoided and treatment options available in Mexico.^{15,16}

Caution should be exercised with homeopathic medicine. Patients may think that natural products are safe, but the use of products such as white willow extract, known as «natural aspirin», produces the same reactions as chemically synthesized aspirin.¹⁹

Very sensitive patients should also avoid cosmetics and foods high in salicylate, in particular

spices and industrially processed foods. *Table 3* lists foods with the salicylate content calculated in mg/kg available in Mexico.^{7,20,21}

DISCUSSION

The AERD, better known as Samter's syndrome, is a complex chronic disease whose most alarming complication is the airway hypersensitivity reaction to aspirin and other non-selective inhibitors of the cyclooxygenase (COX) enzyme in patients diagnosed with chronic rhinosinusitis, nasal polyps, and asthma.^{2,3,22} When collecting the information of these diagnoses in the patient's medical history, the health care professional should also have the clinical suspicion of the disease so that she/he can make a prudent prescribing of painkillers.

There are few management guides and algorithms in the literature recommended for the treatment protocol of patients with AERD. In addition, as Calderon et al. reports, there is a lack of knowledge of the disease even in the medical field.²² This updated review of the literature allows having a simple and practical approach to the disease that will be of help in case of AERD clinical suspicion. The physician will decide whether the patient should be referred to the specialist to treat hypersensitivity reactions to aspirin and other NSAIDs that may progress to more severe complications. Patients with AERD are reported to have a higher morbidity, characterized by more emergency care at the hospital, compared with asthma patients not allergic to aspirin. The identification of this syndrome is critical because of the exacerbations of asthma secondary to aspirin sensitivity that involve not only a significant morbidity but also high economic costs.⁸

Lastly, it would be interesting to have more real data of the Mexican population through epidemiological studies of the AERD and the prevalence of complications due to untimely diagnosis, so that a management protocol could be established with patients having the disease.^{4,8,22}

CONCLUSIONS

1. Education on AERD is paramount for both the patient and health professionals. In dental practice, patients with this pathology are increasingly cared for, so the objective of this review is to study the disease and recognize the first symptoms in order to prevent possible complications (*Table 1*).
2. The stomatologist should be prepared to face the analgesic management of patients with AERD so

as to being able to offer safe alternatives for pain management.

3. The best way to treat a complication is to prevent it, by carefully studying the patients, especially those with a history of specific respiratory signs and symptoms, in addition to researching allergic predisposition and considering AERD as a diagnostic possibility. All this proves useful when it comes to dental care and analgesic prescription.²³
4. Health staff also have the responsibility to educate patients in the knowledge of their disease and the rational use of medicines (NSAIDs) and food or natural products containing salicylates.

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