Clinical Characteristics of Aspirin-Exacerbated Respiratory Disease

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KEYWORDS

• Aspirin • Nonsteroidal anti-inflammatory drugs • Nasal polyposis • Quality of life
• Asthma • Chronic rhinosinusitis • Cyclooxygenase 1

KEY POINTS

- Aspirin-exacerbated respiratory disease presents with characteristic features of adult-onset nasal polyposis, asthma, and hypersensitivity reactions to aspirin or other nonsteroidal anti-inflammatory drugs.
- Aspirin-exacerbated respiratory disease is present in about 7% of all asthmatics and represents a phenotype of more severe sinus disease and asthma.
- Features that suggest a diagnosis of aspirin-exacerbated respiratory disease include severe sinus inflammation on imaging, significant polyp recurrence postoperatively, marked anosmia, and alcohol intolerance.
- There continue to be unmet needs in caring for patients with aspirin-exacerbated respiratory disease. Aspirin is an effective treatment for many, but further treatment options are sought by the patient community.

INTRODUCTION, HISTORICAL NOTES, AND NOMENCLATURE

Aspirin-exacerbated respiratory disease (AERD) was first described in a 1922 French publication by Professors Widal, Abrami, and Lenmoyes.[1] Although only a single case report, their 37-year-old female patient was admitted to the hospital for extensive oral challenges over several weeks. Their description of the patient included all the clinical features of AERD. The patient acquired the disease in her 20s and was plagued by nasal polyposis and asthma, and during oral challenges with tiny quantities of aspirin and antipyrine (the first nonaspirin nonsteroidal anti-inflammatory drug), experienced severe asthma attacks, hives, and rhinorrhea. Oral challenges with non–cyclooxygenase 1 (COX-1)-inhibiting drugs, such as chlorohydrate, urotropine, quinine, and pyramidon,

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Immunol Allergy Clin N Am ■ (2016) ■–■
http://dx.doi.org/10.1016/j.iac.2016.06.002 **immunology.theclinics.com**
0889-8561/16/$ – see front matter

did not induce respiratory or cutaneous reactions. Not knowing any better, the doctors incorrectly called this disease *idiosyncratic anaphylaxis*. Actually, this 37-year-old woman had the first reported case of AERD.

Meanwhile, in the mid-1960s, Professor Max Samter, at the University of Chicago, also identified and described the same disease and, along with Professor Beers, published the first English description of AERD, which he called *aspirin intolerance or triad disease*. This disease then became known as *Samter's syndrome*.[2] At about the same time (1967), a report describing the first positive oral challenges with aspirin, and, on a separate occasion, indomethacin, in a patient with AERD, was published by Vanselow and Smith.[3] It was not until 1993 when Doctor Amy Klion translated Professor Widal's original 1922 case report from French into English,[4] that several investigators realized that Samter's syndrome was actually first described and reported in the literature by Professor Widal. Professors Samter and Beers emphasized and expanded the concept of cross-reactions to nonsteroidal anti-inflammatory drugs (NSAIDs).[5] Over the years, the preferred descriptor for this disease has wandered through a confusing list, including, in addition to Professor Samter's descriptions (intolerance and triad), *aspirin idiosyncrasy*, *aspirin-sensitive rhinosinusitis/asthma*, *aspirin-induced asthma*, *NSAID-induced asthma*, and, finally the 2 currently accepted descriptions, *AERD* in the United States and *NSAID-induced respiratory disease* in Europe. All of these terms describe the disease and not the reactions, which are generally called *acute hypersensitivity reactions to aspirin* (or any NSAID involved in the respiratory reactions).[6]

CLINICAL PRESENTATION

Somewhere around age 30, typical viral respiratory infections develop in otherwise healthy individuals or those with prior allergic rhinitis or asthma. However, unlike the usual clearing of an upper respiratory infection in 2 to 4 weeks, nasal congestion persists.[7,8] Early-onset AERD patients frequently describe their course as, "my cold never went away." A viral infection is one likely culprit in the initiation of AERD. It is possible that after a viral-induced immunologic insult, either anti-inflammatory pathways fail to resolve or epigenetic changes occur, which leads to ongoing irreversible inflammation. Perhaps the virus infection leads to other secondary events such as *Staphylococcus aureas* colonization or other perturbations in the microbiome that could enhance the inflammatory milieu. The true sequence of events in the first few days and weeks of AERD is unfortunately still speculative. It should be pointed out, however, that virus infections are found to enhance type 2 inflammations.[9,10] Alternatively, it is possible that when AERD develops in a healthy individual, the early symptoms are so similar to a viral upper respiratory tract infection that a virus falsely bears the blame. Up to 50% of subjects report a viral illness at the onset AERD.[8] How many viral infections go unreported is of course unknown. Environmental factors such as second-hand cigarette smoke exposure, especially in childhood, seem to increase the risk of AERD development.[11] After AERD is established and begins to evolve, patients subsequently have progressive nasal congestion, anosmia, and eventually pansinusitis with nasal polyposis. In most patients, asthma joins the upper airway disease as the next pathologic event. At this point, patients look like any other person with pansinusitis and asthma. The difference is that a diagnosis of AERD requires both the presence of nasal polyps, sinusitis (and sometimes asthma), plus a respiratory reaction after ingestion of aspirin or any of the NSAIDs that inhibit COX-1. Only then, and not before, is the diagnosis of AERD secure. This NSAID ingestion event can occur at any time in the evolution of the disease.