Aspirin-Exacerbated Respiratory Disease: Clinical Disease and Diagnosis

Grażyna Bochenek, MD, PhD*,
Ewa Niżankowska-Mogilnicka, MD, PhD, FCCP

KEYWORDS

• Aspirin-exacerbated respiratory disease • Aspirin • Aspirin hypersensitivity
• Nonsteroidal anti-inflammatory drugs • Provocation test • Aspirin challenge

KEY POINTS

- Aspirin-exacerbated respiratory disease (AERD) is a distinct clinical syndrome of intractable inflammation of both upper and lower airways, which is characterized by the presence of asthma, chronic eosinophilic rhinosinusitis, nasal polyps, and hypersensitivity reactions to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).
- Exposure to aspirin and other NSAIDs does not initiate the underlying inflammatory process but only exacerbates clinical manifestations of the disease.
- AERD develops according to a distinctive pattern, characterized by a sequence of symptoms: persistent rhinosinusitis, commonly with polyposis, followed by asthma, and then aspirin hypersensitivity.
- Asthma runs a protracted course despite avoidance of aspirin and other NSAIDs.
- Provocation tests with aspirin are the most reliable method to confirm the diagnosis of AERD.

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is a distinct clinical syndrome affecting both upper and lower airways, characterized by the presence of asthma, chronic eosinophilic rhinosinusitis, nasal polyps, and hypersensitivity reactions to cyclooxygenase 1 (COX-1) inhibitors, including aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Exposure to these drugs does not initiate the underlying inflammatory process but only exacerbates clinical manifestations of the disease.

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Department of Pulmonology, Jagiellonian University School of Medicine, Jagiellonian University Medical College, Skawińska 8, Krakow 31-066, Poland
* Corresponding author.
E-mail address: graboch@tlen.pl

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In line with the current classification, AERD belongs to cross-reactive types of hypersensitivity reactions to NSAIDs.[1]

The association of aspirin sensitivity, asthma, and nasal polyposis was described for the first time in 1922 by Widal and colleagues.[2] This syndrome was widely popularized in the late 1960s when Samter and Beers[3,4] described its natural history, and since then it was named *Samter's triad* or *the aspirin triad* (nasal polyps, asthma, and aspirin hypersensitivity). A fourth characteristic, chronic hyperplastic eosinophilic rhinosinusitis, was never mentioned in the description of "triad," but actually makes it a "tetrad"[5] However, neither description is particularly useful, because linkage to the respiratory tract is not disclosed and the original description was not made by Samter in 1968 but rather by Widal in 1922. AERD is now the preferred descriptor in North America and is gaining worldwide acceptance.

PREVALENCE

The prevalence of aspirin hypersensitivity differs with respect to populations studied, diagnostic methods used, and criteria for defining hypersensitivity reactions. It affects 0.6% to 1.9% of the general population.[6–8] The prevalence was found to range from 4.3% to 11% among adult patients with asthma assessed with questionnaires,[6,7,9] and was even higher (21%) when provocation tests were used in patients with asthma and nasal polyposis and chronic rhinosinusitis.[10] In patients with asthma, chronic rhinosinusitis, and nasal polyps, the prevalence of aspirin hypersensitivity confirmed through oral aspirin challenge was found to range from 30% to 40%.[11,12] AERD is rare in children with asthma (2–5%) and is almost never seen before puberty.[10] Women outnumbered men by a ratio of 2.3 to 1 in Europe,[13] and 1.3 to 1 in the United States.[14] Family history of aspirin hypersensitivity was found in 1% to 6% of cases.[13,14] No racial or ethnic predilection to AERD was identified. The disease seems to be underdiagnosed in the population with asthma, because many patients who are aware of the risk of adverse reactions deliberately avoid NSAIDs. However, patients who experience mild NSAID-induced reactions do not associate them with drug ingestion or do not know that NSAIDs may cause asthma attacks.

NATURAL HISTORY

The first symptoms of AERD usually appear between the third and the fourth decade of life.[15] In 2 large cohorts comprising 500 and 300 patients with AERD, the average ages of onset of the disease were 29 and 34 years, respectively.[13,14]

AERD can develop in patients who already have rhinitis and/or asthma or in those who have never had any prior respiratory disease. The clinical presentation is similar worldwide.[13,14] The disease develops according to a distinctive pattern, characterized by a sequence of symptoms: persistent rhinosinusitis, commonly with polyposis, followed by asthma, and then aspirin hypersensitivity. The first clinical manifestation is usually rhinitis, which is related to a flu-like infection. It is characterized by a watery discharge from the nose, nasal blockage, sneezing, and loss of smell. Rhinitis is perennial, difficult to treat, and progresses into a chronic hyperplastic eosinophilic rhinosinusitis often with nasal polyposis. Asthma is usually diagnosed 2 to 3 years later. At about the same time, the first unexpected adverse clinical reaction to aspirin or other NSAIDs occurs in patients who previously tolerated these drugs well. Some patients may have a diverse sequence of symptoms and NSAID-induced respiratory reactions, which are crucial for diagnosing AERD. Despite avoidance of aspirin and other NSAIDs, asthma runs a protracted course.