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Research Paper

The importance of timely diagnosis of aspirin-exacerbated respiratory disease for patient health and safety

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Samter's triad;
Anosmia;
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Aspirin challenge;
NSAID hypersensitivity;
NSAID challenge

Abstract *Backgroud:* Aspirin-exacerbated respiratory disease (AERD) is a difficult-to-treat syndrome where timely diagnosis and initiation of disease-specific therapies are pertinent to improved patient outcomes.
Objective: To characterize the most common timeline for development of the clinical triad [asthma, nasal polyposis, and reactions to nonsteroidal anti-inflammatory drugs (NSAIDs)], identify barriers to prompt diagnosis of AERD, and describe indications for an aspirin challenge to facilitate accurate diagnosis.
Methods: Six hundred ninety-seven patients with diagnosed AERD and history of at least one sinus surgery to remove nasal polyps were identified in the Brigham and Women's Hospital AERD registry. Patient reported age at disease onset of asthma, nasal polyposis, and age of first NSAID reaction were obtained from 2013 to 2019 at enrollment.
Results: Of the 697 patients identified, diagnosis of asthma preceded diagnosis of nasal polyposis and first NSAID reaction, although there was considerable variability between patients.
Conclusions: Prompt diagnosis of AERD is important for patient and provider education and improved care of this difficult-to-treat population of patients. Consider diagnostic aspirin challenge in patients without historical reactions to NSAIDs who have an otherwise compatible clinical history, specifically in patients who take daily low-dose aspirin, leukotriene modifiers,

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avoid NSAIDs, or who are severely symptomatic at baseline where it would be difficult to identify an acute worsening of symptoms.

Aspirin-exacerbated respiratory disease (AERD) is a unique syndrome characterized by the triad of asthma, recurrent sinonasal polyposis, and respiratory reactions to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Accurate and timely diagnosis of AERD is important to ensure patient safety through education and disease awareness, and for the initiation of appropriate disease-tailored therapies.

Unfortunately, we know that a delay in diagnosis is very common for these patients. For some patients, there can be an interval of more than 10 years between the onset of the triad of symptoms and a correct diagnosis.[1] AERD is predominately a disease of adult onset and for many patients the clinical symptoms develop slowly over time. Asthma is usually the first finding, followed by chronic nasal congestion, anosmia, and a diagnosis of nasal polyps within a few years. Through recent investigation of our AERD Patient Registry, we found 697 patients who met the criteria of having been diagnosed with the clinical triad (asthma, nasal polyps, and reactions to NSAIDs) and who had had at least one sinus surgery to remove polyps (Table 1). Among these patients, the average age of asthma onset was 29.6 ± 13.9 years (with 78% of all patients developing asthma as an adult over the age of 18 years old), and the average age of nasal polyp diagnosis was 33.5 ± 11.4 years. Of these patients, there was an average lag time of 3.8 years between the onset of asthma and the onset of nasal polyposis. Although the first reaction to an NSAID was noted on average 2.4 months after being diagnosed with nasal polyps, there was a wide range of timing. Among these patients, 27% of patients noted NSAID reactions prior to a diagnosis of nasal polyps, 45% noted NSAID reactions within one year of the development of nasal polyps, and 28% noted that it had been more than one year after their nasal polyps developed that they first recall an NSAID reaction.

Frustratingly, in a separate study we found that out of 638 patients who had been identified as having all features of the clinical triad listed within their medical record, and then further confirmed as having clinically consistent AERD upon thorough chart review, 12.4% had no diagnosis or mention of AERD or a similar term by any treating caregiver.[2] This suggests that even for patients who are aware of each of their symptoms and report them in a timely manner to their healthcare providers, the diagnosis of AERD is often overlooked.

For many patients with a reliable history of the three clinical components, the diagnosis of AERD can be confidently made based on a consistent medical history. However, there are often patients for whom the diagnosis is not clear at initial presentation, and may require a provocative drug challenge to confirm the diagnosis. Additional findings that are often present and can corroborate the diagnosis of AERD include mild-to-moderate peripheral blood eosinophilia[3] and rapidly recurrent nasal polyps following sinus surgery.[4] A history of alcohol-induced respiratory reactions can provide an additional clue, as 77%–83% of patients with AERD report the development of upper (nasal congestion and rhinorrhea) and/or lower (wheezing, shortness of breath) respiratory symptoms upon consumption of alcoholic beverages.[5,6]

However, relying on a patient-reported history of NSAID allergy can be insufficient for proper diagnosis, as the presence of NSAID hypersensitivity can be difficult to confirm based solely on patient report. Even in 1968 with Samter's initial case series, it was noted that up to 15% of patients with AERD are initially unaware that they are intolerant to aspirin/NSAIDs, or report that they can take NSAIDs without adverse reactions — these patients are not made aware of their drug hypersensivity until a reaction is induced during a formal physician-observed drug provocation test.[7,8] Therefore, it is inappropriate to depend on the patient's response to the simple question of "are you allergic to aspirin or NSAIDs?" We have identified many patients with a delayed diagnosis of AERD because they had answered "no" to this question previously and were never further evaluated.

The patients who require further questioning after answering a single "no" to the aforementioned question generally fall into one of four categories, and a provocative drug challenge is required to establish proper diagnosis of NSAID tolerance or hypersensitivity:

(1) *Patients who have not used NSAIDs recently.* Patients without any recent ingestion of aspirin or NSAIDs may not have used NSAIDs since the development of their

Table 1 Age of onset of asthma, nasal polyps, and reactions to NSAIDs in patients with AERD.

Age in years of first diagnosis of	Asthma (years, Mean ± Stdev)	Nasal polyps (years, 'Mean ± Stdev)	1 st NSAID reaction (years, Mean ± Stdev)
All (n = 697)	29.6 ± 13.9	33.5 ± 11.4	33.7 ± 12.2
Time between asthma and NP diagnosis	_	3.8 ± 11.4	_
Time between NP diagnosis and first NSAID reaction	_	_	0.2 ± 6.6

respiratory disease. However, without recent NSAID exposure, they may be unaware that they have developed NSAID hypersensitivity. A formal provocative drug challenge is required for diagnosis.

(2) *Patients' NSAID-induced symptoms may be pharmacologically blocked.* The regular use of leukotriene-modifying drugs for asthma control, such as the leukotriene receptor antagonist, montelukast, or the 5-lipooxygenase inhibitor, zileuton, can diminish or block the symptoms of NSAID-induced reactions.[9,10] Therefore, for patients on a leukotriene-modifying drug, we recommend these medications are stopped at least 7 days prior to a provocative drug challenge. We also ask patients to discontinue antihistamine use 7 days prior to provocative drug challenge as these medications may also mask a potential response.[11] Omalizumab has also been reported to inhibit NSAID-induced reaction symptoms[12] and other newly available biologics are under investigation for their reaction-blocking properties as well. It is not yet clear how long of a washout period will be required in order to trust the results of a provocative drug challenge in these cases.

(3) *Patients who are not aware of their own reaction symptoms.* There are some particularly stoic patients with AERD who present with both asthma and recurrent nasal polyps, but maintain that they can use aspirin or NSAIDs without developing adverse reactions. This general insensitivity to reaction symptoms seems to occur in patients with the most severe chronic sinus disease, who apparently have become accustomed to their chronic state and do not notice acutely worsening symptoms that follow NSAID ingestion. For patients with chronic, complete nasal obstruction, intermittent episodes of worsened nasal congestion may go unnoticed. Therefore, a formal provocative drug challenge with objective measures can be helpful.

(4) *Patients on daily low-dose aspirin for cardiac prevention.* We have found that a subset of patients with AERD who currently taking 81 mg of aspirin for cardiac protection at the time of initial clinical evaluation do not report symptoms of NSAID-induced hypersensitivity. These patients, who usually have very mild asthma symptoms, historically tolerate low-dose aspirin, but after stopping low-dose aspirin for at least 10 days, develop aspirin-induced respiratory symptoms during a provocative oral aspirin challenge.[1] Their tolerance of low-dose aspirin may attributed to unnoticed, mild aspirin-induced symptoms upon starting low-dose aspirin or because initiating low-dose aspirin induced a state of desensitization before the development of their respiratory disease.

Early diagnosis of AERD is crucial for three main reasons: (1) a careful understanding of how to avoid all medications that fall within the class of cyclooxygenase-1 inhibitors is a key to patient safety, (2) proper diagnosis is required to allow patients to pursue disease-tailored therapies, and (3) education regarding alternative non-cyclooxygenase-1 inhibiting pain-relief agents can help to prevent the future overuse of opioids.

First, we must be willing to dedicate time to a thorough, educational conversation with AERD patients in order to provide accurate patient and provider education about avoiding NSAIDs. A recent study by our group demonstrated that nearly 1 in 4 patients with AERD had accidently ingested an NSAID and developed a reaction, after being diagnosed with AERD, and that those subsequent reactions can be life threatening. Furthermore, in almost 25% of those episodes, the ingested NSAID had been prescribed to the patient by a physician, indicating the need for improved patient and provider education about NSAID avoidance.[13]

Second, there are now several treatment modalities that are either specific to AERD or are known to be more efficacious in patients with AERD. The only true disease-specific therapy for AERD is aspirin desensitization to initiate high-dose daily aspirin, which provides long-term therapeutic benefit for the majority of patients with AERD.[4,14–17] However, there are other available treatments that may be appropriate for the management of AERD as well. For example, zileuton provides greater improvements in pulmonary function for patients with AERD compared to patients with aspirin-tolerant asthma and should be considered for the treatment of uncontrolled asthma in AERD.[18] Additionally, the IL-4Rα blockade afforded by dupilumab appears to be particularly efficacious for the improvement of nasal polyp burden and asthma control in AERD.[19]

Finally, the presence of a reported NSAID hypersensitivity increases the odds of receiving an opioid prescription when compared to patients who are NSAID tolerant.[20] Therefore, for NSAID-allergic patients with pain-management needs, a targeted evaluation by an allergist may be helpful to provide alternative analgesic options. As celecoxib is tolerated by nearly all patients with AERD, this cyclooxygenase-2 inhibitor could be a safe alternative to provide control of inflammation and pain.[21]

In summary, confirming the diagnosis of AERD can be challenging in some patients, but the ability of health care providers to recognize symptoms and ask pointed questions will likely lead to timely diagnosis. For many patients with AERD, a diagnosis may be made based on compatible clinical history. However, certain patients require a formal aspirin challenge to confirm the diagnosis. Formal physician-observed challenges should be pursued for patients who have not recently ingested aspirin or NSAIDs, are currently on a leukotriene blockade or 81 mg daily aspirin therapy, or who have severe symptoms at baseline and may not perceive an acute change in symptoms following aspirin or NSAID ingestion. Timely diagnosis of AERD allows for earlier and increased opportunities for patient and collaborating physician education, initiation of disease-specific therapies, and ultimately improved patient safety.

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Declaration of competing interest

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