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Longitudinal progression of aspirin-exacerbated respiratory disease: analysis of a national insurance claims database

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Abstract

Background: Aspirin-exacerbated respiratory disease (AERD) is a recalcitrant inflammatory disorder defined by asthma, nasal polyposis, and sensitivity to cyclooxygenase-1 inhibitors. The timeline and course of disease progression is unclear.

Methods: The Truven MarketScan Database, a large American health insurance claims repository, was queried to identify patients meeting criteria for AERD from 2009 to 2015. Included patients had associated International Classification of Diseases, 9th edition (ICD-9) codes consistent with all 3 components of AERD: asthma, nasal polyposis, and drug allergy. Patterns of disease onset and time to progression were analyzed.

Results: A total of 5628 patients were identified for study inclusion. Of the 3 components of AERD, 3303 patients (59%) were initially diagnosed with asthma, 1408 (25%) were initially diagnosed with nasal polyps, and 917 (16%) were first diagnosed with drug sensitivity. The most common (36%) sequence of diagnoses was asthma, followed by nasal polyps, followed by drug allergy. The median interval between diagnosis of upper or lower airway involvement (ie, nasal polyps and/or asthma) to recognition of drug sensitivity was 259 days (quartiles Q1 to Q3: 92 to 603 days). In patients with both asthma and nasal polyps diagnoses, the risk of developing drug sensitivity during the study time period was 6%.

Conclusion: Upper and lower airway disease is often initially recognized in patients with AERD, whereas drug sensitivity presents month to years later. This delay may be due to the pathophysiology of AERD and disease progression or due to practice patterns in diagnostic testing and coding. Further work is warranted to identify these patients at early stages in their disease progression. © 2019 ARS-AAOA, LLC.

Keywords

asthma; chronic rhinosinusitis; aspirin-exacerbated respiratory disease; AERD; allergens; nasal polyps

Aspirin-exacerbated respiratory disease (AERD) is defined as the coexistence of 3 diagnoses: asthma, nasal polyposis, and sensitivity to cyclooxygenase (COX-1) inhibitors. The disease is more common in women and is thought to affect between 0.6% and 2.5% of the general population and 7% of asthmatic patients.^{1,2} The pathophysiology of the disease is thought to be an enhanced response to COX-1 inhibition. However, AERD patients show elevated cysteinyl leukotriene (LT)E₄ levels even at baseline.³

Many questions remain regarding the pathophysiology of AERD. The timeline and natural progression of AERD is not well studied. Previous work has suggested that patients initially note rhinitis, followed approximately 2 years later by asthma, and then 4 years later by aspirin or nonsteroidal anti-inflammatory drug (NSAID) sensitivity; however, the true diagnoses of nasal polyps and aspirin sensitivity are dependent on evaluation by subspecialty services.^{1,4} Although rhinitis was a common initial complaint in a previous survey study,⁴ patients are often not evaluated by an otolaryngologist early on in their disease progression when rhinitis is the only symptom present. Therefore, this estimated time-line is limited by diagnostic testing practices. Diagnosis may be further delayed because of lack of exposure to aspirin or NSAIDs for many patients. The average age of diagnosis of AERD was noted to be 34 years in a study confirming drug sensitivity by oral aspirin challenges.⁵

Treatment options for AERD include medical management of asthma and sinus disease, surgery for nasal polyps, and aspirin avoidance or desensitization. Newer monoclonal antibody therapies are also recently being evaluated and employed in these patients. Early recognition of AERD and appropriate medical intervention or aspirin desensitization to initiate high-dose aspirin treatment may decrease polyp growth or regrowth.³ Because of the rarity of this disease, inconsistencies with diagnostic practices, and lack of generalized accessibility to desensitization centers, many questions remain unanswered regarding the disease progression and appropriate treatment for AERD.

The MarketScan database is a repository of both private and Medicare-reported claims (Truven Health Analytics, part of the IBM Watson Health™ business, Ann Arbor, MI).⁶ Over 20 billion patient encounters are available between the years of 2009 and 2015. Through the use of International Classification of Diseases, 9th edition (ICD-9) and Current Procedural Terminology (CPT) coding evaluation, the database can be easily queried for diagnoses, procedures, and treatment of included patients. In hopes of better understanding the progression of AERD and current practices for these patients, the aim of this study was to evaluate the AERD cohort within the MarketScan database in regard to timing of diagnoses.

Materials and methods

The MarketScan Database was queried to identify patients with AERD from January 1, 2009, to October 1, 2015. We included patients with associated ICD-9 diagnosis codes consistent with all 3 components of AERD: asthma, nasal polyposis, and drug allergy, as a more specific aspirin or NSAID allergy code is not available in the ICD-9 system. ICD-9 codes for other lung diseases and immunodeficiency were excluded. This strategy was modeled after an algorithm recently published by Cahill et al.⁷ in which an automated search based on ICD-9 coding for asthma and nasal polyps and electronic health record drug allergy listing was confirmed to have an 89% positive predictive value for AERD when verified by comprehensive chart review. We analyzed the time of first occurrence for each diagnosis.

Results

A total of 5628 patients met criteria for study inclusion. The average \pm standard deviation (SD) age was 46 ± 11 years, with 60% being female (Table 1). Of the 3 components of AERD, 3303 patients (59%) were initially diagnosed with asthma, 1408 (25%) were initially diagnosed with nasal polyps, and 917 (16%) were first diagnosed with drug allergy (Table 1).

The most common sequence of diagnoses, seen in 36% of patients, was initial diagnosis of asthma, followed by nasal polyps, followed by drug allergy. The least common timeline of sequence of diagnoses was the reverse order, seen only in 6% of patients: initial diagnosis of drug allergy, followed by nasal polyps, followed by asthma (Table 2).

Among those patients who were not diagnosed with drug allergy first, the median time interval between diagnosis of either upper or lower airway involvement (ie, nasal polyps and/or asthma) to recognition of drug allergy was 259 days (quartiles Q1 to Q3: 92 to 603 days).

For all patients with both asthma and nasal polyp diagnoses before April 1, 2015, and who did not have drug allergy diagnosed first ($n = 2478$), the risk of developing drug allergy during the study time period was 6%.

Discussion

In this analysis of a comprehensive insurance claims database from the United States, we determined that patients within the AERD cohort were most commonly first diagnosed with asthma, followed by nasal polyps, and finally by drug allergy. The median length of time to development of drug allergy, following an upper or lower airway diagnosis was 259 days, or almost 9 months. Patients with both asthma and polyp diagnoses had a 6% chance of developing drug allergy during the study time period. Although previous work is generally in line with these findings regarding order of diagnoses within this triad (ie, upper/lower airway symptoms generally present before diagnosis of drug sensitivity), to our knowledge, this is the largest study to report these diagnostic patterns in AERD. Approximately 60% of our AERD cohort was found to be female. This is also consistent with previous work.¹ The average age of the patients in our AERD cohort was slightly older than previously published

work.¹ This may be due to the fact that specific coding for drug sensitivity was required, as clinical documentation of reported sensitivity was not sufficient for inclusion and could not be identified in the MarketScan database. This limitation, as well as study duration of 6 years, likely contributed to an incidence of only 6% of asthma and nasal polyp patients developing drug allergy, which is lower than previously published prevalence rates of aspirin sensitivity in patients in this risk group.⁸

The results of this study suggest that the progression of AERD is defined by initial lower airway disease, followed by sinonasal involvement, and last by drug intolerance. This natural progression of disease needs to be verified by prospective studies as the results of this study may be biased by diagnostic practices. Arguably, within the triad of AERD symptoms, asthma is the most straightforward to diagnose across medical providers in general, likely explanatory for the results in our study. Although authors have suggested that rhinitis and congestion are actually the initial symptoms in AERD,¹ because of delay in access to nasal endoscopy, the diagnosis of polyps may come after a documentation of asthma. Similarly, aspirin challenge requires subspecialty referral and potential cost, limiting the convenience of this diagnostic assessment. However, given that baseline arachidonic acid metabolism is abnormal in AERD patients prior to aspirin provocation,^{9,10} it is likely that the predisposition to NSAID sensitivity precedes or is concurrent with the development of asthma and nasal polyps. In fact, this predisposition may be directly associated with asthma and nasal symptoms, and may progress to airway symptoms as aspirin sensitivity worsens. Physicians should consider the possibility of AERD even in patients who have not yet met diagnostic criteria, in hopes of early identification and slowing the progression of disease. The utility of aspirin challenge prior to convincing history of aspirin sensitivity symptoms is not well documented because of a lack of predictive biomarkers to identify patients who are at risk for AERD but have not experienced an adverse drug reaction. White et al.¹¹ described a subset of patients in which initial aspirin challenge was negative, but AERD was confirmed on repeat challenge. Whether this finding is due to progression of disease or limited sensitivity of the diagnostic test is unclear.

There are several limitations of this study. A limitation of all AERD research is the requirement of specific diagnostic testing to verify clinical symptoms, such as nasal endoscopy and aspirin challenge. These procedures may not be available to patients because of cost or lack of physician accessibility, and therefore our cohort of patients is likely not fully representative of the AERD population. The MarketScan database is limited by reliance on physician coding and documentation, and the inclusion of a subset of possible insurance providers. Because chart review is not possible in this de-identified dataset, we are limited by lack of information regarding symptoms, which may precede documentation by diagnostic coding. Because of the lack of a specific code for AERD, we are also limited by the proposed algorithm to best capture patients. ICD-9 codes for drug allergy were used as a proxy for aspirin allergy due to lack of specific coding available for aspirin sensitivity, which is an additional limitation of the proposed AERD cohort. Last, the MarketScan database contains information from 2009 to 2015, and patients diagnosed outside of this timeframe were not included. However, we believe that our study is proportionally representative of the actual AERD population and that diagnostic and treatment patterns can be inferred from this study.

Future directions for this area of research include prospective studies to evaluate the possibility of AERD diagnosis in patients with either asthma and/or nasal polyps through aspirin challenge, even prior to reported clinical aspirin sensitivity. An earlier diagnosis of aspirin sensitivity with avoidance of triggers or aspirin desensitization may dampen the progression of disease. A better understanding of the pathophysiology and natural progression of symptoms will lead to improved prevention and treatment of AERD.

Conclusion

Upper and lower airway disease is often initially recognized in patients with AERD, whereas diagnosis of aspirin sensitivity occurs in a delayed fashion. This delay may be due to the pathophysiology of AERD and disease progression or due to practice patterns in diagnostic testing. Future work to better understand the AERD disease process will improve diagnostic testing practices and treatment.

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TABLE 1.

Demographics of cohort

Cohort	Value
Total cohort, n	5628
Female, n (%)	2230 (60)
Age (years), mean \pm SD	46 \pm 11
Initial diagnosis, n (%)	
Asthma	3303 (59)
Nasal polyps	1408 (25)
Drug allergy	917 (16)

SD = standard deviation.

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TABLE 2.

Sequence of diagnoses

Sequence	n (%)
Asthma, nasal polyps, drug sensitivity	2002 (36)
Asthma, drug sensitivity, nasal polyps	1301 (23)
Nasal polyps, asthma, drug sensitivity	959 (17)
Drug sensitivity, asthma, nasal polyps	584 (10)
Nasal polyps, drug sensitivity, asthma	449 (8)
Drug sensitivity, nasal polyps, asthma	333 (6)

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