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Aspirin-exacerbated respiratory disease: not always "adult-onset"

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To the Editor

Aspirin-exacerbated respiratory disease (AERD) is a syndrome characterized by the triad of chronic rhinosinusitis with eosinophilic nasal polyposis, asthma, and respiratory reactions to cyclooxygenase-1 (COX-1) inhibitors. The pathogenesis of AERD has not been fully elucidated, but it is likely driven in part by the overproduction of cysteinyl leukotrienes.[1] Aspirin challenge-induced respiratory reactions, which often include both upper and lower respiratory symptoms, are pathognomonic of AERD. Treatment modalities include aspirin desensitization and subsequent daily aspirin therapy, leukotriene receptor antagonists (LTRAs), and zileuton, a 5-lipoxygenase (5-LO) inhibitor. Both zileuton and LTRAs improve asthma control and sinonasal symptoms in patients with AERD[2,3], however respondents to a recent patient survey identified zileuton as "extremely effective" more often than LTRAs.[4]

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The prevalence of AERD is approximately 7% in adult patients with asthma and 14% in those with severe asthma, with the typical age of onset greater than eighteen years.[5] However, in our AERD patient registry, 3.5% of the patients (8 of 227) reported that they developed nasal polyps, and presumably the initial onset of disease, prior to age eighteen. Two previous studies determined the incidence of aspirin intolerance in the pediatric asthma population by oral aspirin challenge to be 13-28%,[6,7] but these studies excluded patients with nasal polyposis and therefore are limited with respect to the current definition of AERD as they did not include patients with the full triad of symptoms. A recent retrospective case study described ten adolescent patients with aspirin-sensitive asthma; all were noted to have a mild asthma phenotype and developed prominent extra-respiratory features during aspirin challenge, but only 2 of the 10 patients had nasal polyposis.[8] With this literature in mind, we present three pediatric cases of AERD with the full triad of symptoms, and detail their diagnostic work-up and treatment regimens.

A 12-year-old female presented with a two-year history of moderate persistent asthma and chronic rhinosinusitis. She required multiple courses of oral steroids for rhinosinusitis and eventually underwent endoscopic sinus surgery. Post-operatively, she developed rapidly-growing nasal polyps. There was no report of COX-1 inhibitor intolerance, although she had used these medications infrequently. An oral aspirin challenge was performed and she developed urticaria, cough, nasal congestion, and decrease in FEV1 during the challenge. Following symptom resolution, aspirin dosing was continued to achieve desensitization. The patient's laboratory studies are summarized in Table 1; cysteinyl leukotriene metabolites were not measured. Results of the aspirin challenge are detailed in Table 2. The patient was previously treated with inhaled fluticasone and oral cetirizine. Aspirin therapy was initiated after desensitization; her cough frequency decreased on 650 mg twice daily aspirin, but her nasal congestion and rhinorrhea did not improve.

A seven-year-old female presented with history of severe persistent asthma, systemic reactions to ibuprofen, and recurrent episodes of dyspnea, urticaria, diarrhea, and abdominal pain. Nasal polyps were diagnosed at eight years old. Laboratory studies detailed in Table 1 were significant for peripheral eosinophilia, elevated serum tryptase, and elevated urinary prostaglandin D2, 11β prostaglandin F2α, and histamine. The patient's treatment regimen initially consisted of fluticasone propionate/salmeterol, montelukast, fexofenadine, and ranitidine, which were not sufficient to control her symptoms. She underwent aspirin desensitization, which induced nasal congestion, bronchoconstriction, and decrease in FEV1, as summarized in Table 2. Aspirin was increased to 650 mg twice daily after desensitization; polyps were not visualized on repeat examinations. However, daily aspirin therapy was discontinued due to debilitating urticaria necessitating near constant corticosteroid use; zileuton was added, which dramatically improved her urticaria. No polyp regrowth has been noted in the past 1.5 years. Given this patient's continued corticosteroid requirement, a trial of mepolizumab is currently underway.

A sixteen-year-old female presented with a history of severe persistent asthma, rhinosinusitis, nasal polyposis, vocal cord dysfunction, and a systemic reaction to ketorolac. From age fourteen to sixteen, she had recurrent_episodes of wheezing, vomiting, and abdominal pain requiring multiple hospitalizations. The patient's laboratory studies, detailed

in Table 1, were significant for peripheral eosinophilia, elevated urinary prostaglandin D2, and elevated serum IL5 and IL13. The patient underwent two COX-1 inhibitor desensitizations at age sixteen, summarized in Table 2. After the first aspirin desensitization, this patient's treatment regimen consisted of fluticasone/salmeterol, ranitidine, cetirizine, montelukast, and aspirin. Daily aspirin therapy was initially associated with a decrease in the patient's bronchodilator requirement, however nasal congestion, abdominal pain, and urticaria persisted. This patient underwent nasal polypectomy at age sixteen; daily aspirin therapy was discontinued prior to surgery. A second desensitization was attempted, but was halted after intranasal ketorolac resulted in severe hypoxemic respiratory distress and patient required multiple doses of epinephrine. Her regimen was transitioned to budesonide/formoterol fumarate, zafirlukast, zileuton, cetirizine, and ranitidine and no polyp regrowth has been noted in the past year. Due to poor asthma control on maximal therapy (requiring daily albuterol), the patient was started on mepolizumab at age seventeen, three months prior to manuscript submission.

We report a case series of three patients with AERD with onset of disease prior to age eighteen. These cases highlight that the diagnosis of AERD should be considered in pediatric asthmatic patients with nasal polyps, and that an aspirin challenge may be required to confirm the diagnosis. We recommend that pediatric AERD patients should be trialed on 5-LO inhibition with zileuton, which is approved for use in patients ages twelve and above. The addition of high-dose aspirin therapy should also be discussed, although the efficacy of high-dose aspirin in the pediatric AERD population has never been investigated, and potential risk of Reye's syndrome should be considered.

This case series contributes novel data as patients 2 and 3 have a severe phenotype and prominent extra-respiratory symptoms despite leukotriene inhibition and high-dose aspirin therapy, unlike the mild cases previously reported in adolescents.[8] It is notable that AERD is typified by eosinophilic inflammation and patients 2 and 3 have peripheral eosinophilia and patient 3 has elevated serum levels of both IL5 and IL13. The disease manifestations of these two pediatric patients are very similar to a recently described subset of adult patients with severe AERD who develop gastrointestinal and skin symptoms during aspirin challenges and who were found to dramatically overproduce prostaglandin D2.[9] Mepolizumab, a humanized IL5 monoclonal antibody, is currently being trialed in patients 2 and 3 and has been previously shown to reduce nasal polyp size in adult patients with AERD.[10] These cases illustrate that as the pathogenesis of this disease becomes clearer, future research should be conducted to expand disease-targeted therapy in AERD.

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Abbreviations

AERD	aspirin-exacerbated respiratory disease
COX-1	cyclooxygenase-1
5-LO	5-lipoxygenase, LTRA, leukotriene receptor antagonist
IU	international units
mg	milligram
ng	nanogram
pg	picogram
mL	milliliter
dL	deciliter

Clinical Implications Box

Aspirin-exacerbated respiratory disease (AERD) should be considered and evaluated in pediatric asthma patients with nasal polyps and/or COX-1 inhibitor intolerance. An aspirin challenge may be required to confirm the diagnosis and disease-targeted therapies are available for children with AERD.

Table 1

Selected historical and laboratory values from three pediatric AERD cases.

	Patient 1	Patient 2	Patient 3
Age of nasal polyps (years)	11	8	13
Age of asthma diagnosis (years)	10	7	4
Age of COX-1 inhibitor reaction (years)	11 (aspirin)	7 (ibuprofen)	16 (ketorolac)
COX-1 inhibitor reaction	Respiratory	Respiratory	Respiratory
Age of menarche (years)	11	Pre-menarche	13
Asthma maintenance therapy (inhaled)	Fluticasone propionate	Fluticasone propionate/salmeterol	Budesonide/formoterol fumarate
Absolute Eosinophil Count (range: 0.02-0.32 K/uL)	0.13	0.01-0.99 *	0.29-3.69 *
Immunoglobin E (range: 0-100 IU/mL)	45	463 *	351 *
Urine prostaglandin D2 (range: 100-280 ng/24 hours)	-	1821 *	832 *
Urine 11β prostaglandin F2α (range: 0-1000 ng/24 hours)	-	2345 *	-
Urine histamine (range: 0-386 nmol/g of creatinine)	-	423 *	-
Serum IL5 (range: <5 pg/mL)	-	-	98 *
Serum IL13 (range: <5 pg/mL)	-	-	19 *
Serum tryptase, baseline (range: 0-11.7 ng/mL)	8.2	9.6	3.0
Serum tryptase, during systemic reaction to COX-1 inhibitor (range: 0-11.7ng/mL)	-	48.5 *	26.9-86.1 *
CD117 staining (bone marrow biopsy)	-	Negative	Negative
Cytogenetics (PDGFRA1, PDGFRAB or FGFR1)	-	Normal	Normal
C-kit mutation (D816V)		Negative	Negative

-: not measured or performed.

*elevated values.

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Table 2

Aspirin challenge results from three pediatric AERD cases; patient 3 underwent two aspirin challenges. All patients completed aspirin desensitization.

		Patient 1	Patient 2	Patient 3 (1)	Patient 3 (2)
Pre-challenge FVC (% predicted)		106%	94%	111%	50%
Pre-challenge FEV1 (% predicted)		59%	100%	105%	50%
1.26 mg intranasal ketorolac 2.52 mg intranasal ketorolac 5.04 mg intranasal ketorolac	FEV1	-	-	100%	60%
	Symptoms	-	-	None	None
	FEV1	-	-	101%	68%
	Symptoms	-	-	Nasal stinging	Sneezing
	FEV1	-	-	105%	60%
	Symptoms	-	-	None	Rhinorrhea, sneezing, ear pruritus, improved with cetirizine
7.56 mg intranasal ketorolac	FEV1	-	-	51-55%	-
	Symptoms	-	-	Abdominal pain	Vomiting, abdominal pain, severe hypoxic respiratory distress requiring 9 epinephrine doses and continuous albuterol (challenge stopped and admitted to PICU)
40-60 mg aspirin	FEV1	45%	100%	30-31%	-
	Symptoms	Urticaria, self-resolved	None	Inspiratory stridor, urticaria, lip edema, emesis. Challenge paused, improved with albuterol, diphenhydramine and PFTs. Patient then further desensitized	-
80 mg aspirin	FEV1	48%	73%	-	-
	Symptoms	Urticaria, self-resolved	Nasal congestion, wheezing. Patient then further desensitized	-	-
162 mg aspirin	FEV1	48%	-	-	-
	Symptoms	Nasal congestion, cough, rhinorrhea, improved with zileuton. Tolerated repeat 162mg dose	-	-	-

- not measured or performed.