

Nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease in adolescents

Hacer Ilbilge Ertoyl Karagol, MD¹, Ozlem Yilmaz, MD¹, Erdem Topal, MD¹, Alper Ceylan, Prof² and Arzu Bakirtas, Prof¹

Background: There has been no study investigating non-steroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (NERD) exclusively in childhood. Therefore, in the current study, the authors aimed to evaluate the diagnostic features, clinical characteristics, and follow-up of adolescents diagnosed with NERD.

Methods: The patients who were consecutively diagnosed with NERD between January 2011, and November 2013, included in the study. Oral provocation test (OPT) with at least 2 different NSAIDs was used to confirm NSAID hypersensitivity in patients with underlying asthma/chronic rhinosinusitis/nasal polyps. All patients were followed regularly in 3-month intervals by the Pediatric Allergy and Otorhinolaryngology Department for asthma, allergic rhinitis, or chronic rhinosinusitis with or without nasal polyps.

Results: A total of 10 adolescents with NERD were included in the study. The mean age of the patients at the time of diagnosis was 14.9 ± 1.5 years. Hives or angioedema accompanied respiratory complaints induced by NSAIDs. The mean duration of follow-up was 28.9 ± 12.4 months. All patients had asthma except 1 with asymptomatic bronchial hyperre-

activity. Asthma of patients was well-controlled with moderate dose of inhaled corticosteroids. Chronic rhinosinusitis with or without nasal polyps developed in 2 patients. Aspirin desensitization was required in these 2 patients with recurrent nasal polyps.

Conclusion: NERD in childhood has much more favorable clinical characteristics and course than in adulthood. Few adolescents with NERD refer with typical chronic upper respiratory tract complaints. The asthma component seems to be mild and is well controlled in the short-term follow-up. © 2015 ARS-AAOA, LLC.

Key Words:

NSAIDs-exacerbated respiratory disease; adolescents; follow-up; NERD; nonsteroidal anti-inflammatory drug

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Nonsteroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (NERD), which was previously known as Widal syndrome, aspirin triad, Samter's syndrome, aspirin-induced asthma, aspirin-intolerant asthma, and aspirin-exacerbated respiratory disease, was renamed by the last task force.¹ This type of hypersensitivity reaction induced by aspirin or other NSAIDs

manifests primarily as bronchial obstruction, dyspnea, and nasal congestion/rhinorrhea in patients with underlying chronic airway diseases such as asthma/rhinosinusitis/nasal polyps.¹ This is a well-recognized clinical phenomenon in described in adults after the third decade of life.²⁻⁴ Data related to cases in childhood is present within studies investigating aspirin intolerance in children with asthma at the beginning of the 1980s.^{5,6} In addition to case reports as "Samter's triad,"^{7,8} NERD has not been studied exclusively in children. Therefore, in the current study, the authors aimed to evaluate the diagnostic features, clinical characteristics, and follow-up of children and adolescents diagnosed with NERD.

Patients and methods

Patients

This retrospective observational case study was performed in the outpatient clinic of the Pediatric Allergy and Asthma

¹Department of Pediatric Allergy and Asthma, Gazi University School of Medicine, Ankara, Turkey; ²Department of Otorhinolaryngology-Head and Neck Surgery, Gazi University School of Medicine, Ankara, Turkey

Correspondence to: Hacer Ilbilge Ertoyl Karagol, MD, Gazi University, School of Medicine, Department of Pediatric Allergy and Asthma, 06510 Beşevler, Ankara, Turkey; e-mail: theilbilge@yahoo.com.au

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Unit of Gazi University Hospital. All consecutive patients diagnosed with NERD between January 1, 2011, and November 1, 2013, were included. Baseline demographic and clinical characteristics, including age, gender, duration of asthma symptoms, pulmonary function tests, aeroallergen sensitizations, serum eosinophil counts, history of rhinosinusitis/nasal polyps, and analgesic intolerance were recorded.

Definitions

NERD

The diagnosis of NERD in patients who defined reactions with NSAIDs in the presence of underlying asthma/chronic rhinosinusitis (CRS)/nasal polyps, was established with the development of 1 or more of the defined reactions below during an oral provocation test (OPT), which was conducted with at least 2 different NSAIDs.^{1,9} Reactions that were accepted as positive included: (1) naso-ocular reactions only, such as itching, sneezing, congestion, epiphora, and conjunctivitis; (2) naso-ocular and >15% decline in forced expiratory volume in 1 second (FEV₁); (3) lower respiratory reaction only (FEV₁ decline of >20%); (4) laryngospasm with or without (1), (2), or (3) (flat or notched inspiratory curve); (5) systemic reaction: hives, angioedema, flushing, gastric pain, and hypotension with (1), (2), (3), and (4).⁹

In patients who had reactions to a single NSAID in the history, OPT was conducted with aspirin along with the suspected drug. Provocation tests were conducted according to OPT procedure, which was previously defined in the study of Yilmaz et al.¹⁰ During the OPT, 4 or 5 escalating doses of the culprit NSAID were administered at intervals of 60 minutes up to the maximum single dose of the specific drug. The challenge doses were modified according to the weight of children when needed (Table 1).

Asthma

Asthma was defined as recurrent episodes of wheezing and/or dyspnea that responded to inhaled beta₂-agonists, or bronchodilator responsiveness documented on spirometry ($\geq 12\%$ change in FEV₁ predicted after 400 μ g salbutamol) or bronchial hyperreactivity.¹¹ The severity and control level of asthma was also determined according to the guidelines.¹¹

Allergic rhinitis

Allergic rhinitis is clinically defined by the occurrence of symptoms such as rhinorrhea, nasal obstruction, nasal itching, and sneezing for at least 2 years in children with clinically relevant aeroallergen sensitivity.¹²

CRS

Definition of CRS was based on the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) diagnostic criteria: an inflammation of the nose and the paranasal

TABLE 1. Drug dosages for OPT

Drug name	Provocation doses (mg)	Maximum daily doses (mg/kg/day)
Diagnostic purposes		
Acetaminophen	10, 50, 250, 500	60
Aspirin	10, 20, 50, 100, 200	40
Diclofenac sodium	10, 20, 50, 70	3
Flurbiprofen	10, 25, 75, 100	300 mg/day
Ibuprofen	10, 20, 80, 150, 300	40
Metamizole sodium	62.5, 125, 250,	66
Naproxen sodium	10, 20, 50, 150, 275	7
Safe alternative		
Nimesulide	25, 75, 100	
Meloxicam	2.5, 5, 7.5	

OPT = oral provocation test.

sinuses characterized by at least 12 weeks of at least 2 symptoms, such as nasal blockage/obstruction/congestion, nasal discharge (anterior/posterior nasal drip), facial pain/pressure, and/or reduction or loss of smell, and either endoscopic signs of disease and/or relevant computed tomography (CT) scan changes.¹³

Atopy was determined with a standard panel of skin-prick tests and was considered positive if the mean wheal diameter was ≥ 3 mm compared with negative control. Immune deficiencies, cystic fibrosis, and cilia dyskinesia were excluded by pediatric pulmonology and immunology departments.

All patients were followed regularly in 3-month intervals by the pediatric allergy and otorhinolaryngology department for asthma, allergic rhinitis, and CRS with or without nasal polyps. In the follow-up, clinical data including pulmonary function tests, the level of asthma control, the number and dates of sinus surgery and/or polypectomies; medical treatments of asthma and rhinosinusitis were recorded. The number of hospitalizations, emergency department (ED) visits and use of systemic corticosteroid regimens for asthma were also entered to the database. The study was approved by the ethics committee of Gazi University Hospital and written informed consent was obtained from all patient and/or their parents.

Aspirin desensitization

Aspirin desensitization was performed according to the protocol by Lee and Stevenson¹⁴ by oral route. In Turkey, aspirin is commercially available in 100-mg, 300-mg, and 500-mg tablets; therefore, the doses were arranged by splitting the aspirin tablets.

TABLE 2. Demographics and laboratory characteristics of the study group (n = 10)*

Age at onset of asthma (years), mean $\pm$ SD	10.1 $\pm$ 3.5
Duration of asthma (years), mean $\pm$ SD	4.6 $\pm$ 2.9
Duration of NSAIDs intolerance (years)	2 (0.1–9)
BMI, kg/m ² , mean $\pm$ SD	20.7 $\pm$ 2.5
Emergency department visits for asthma ^a	0 (0–6)
Hospitalizations for asthma ^a	0 (0–3)
Systemic corticosteroid regimens use ^a	0 (0–4)
Baseline FEV1 (% predicted)	117.5 (83–122)
Baseline MEF25–75 (% predicted), mean $\pm$ SD	118.5 $\pm$ 31.3
Baseline blood eosinophil count	280.5 (100–1000)

*Values for continuous variables are median (minimum–maximum).

^aFor the duration of asthma.

BMI = body mass index; FEV1 = forced expiratory volume in 1 second; MEF25–75 = maximal expiratory flow at 25% to 75%; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation.

OPT to find safe alternative

OPTs were performed to find safe alternatives in children with confirmed NERD. The relatively COX-2 selective inhibitors nimesulide and meloxicam were challenged as safe alternative NSAIDs. We tried nimesulide as the first drug and if the patient reacted to it, meloxicam was tried as the second choice.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 15.0 software (SPSS, Inc., Chicago, IL). A descriptive analysis was used for the characterization of patients. Descriptive statistics were expressed as frequency and percentage for categorical variables, whereas quantitative data were expressed as mean $\pm$ standard deviation (SD) for normally distributed variables and median (minimum to maximum) for non-normally distributed data.

Results

Demographic data and presenting symptoms

A total of 10 adolescents with NERD were included in the study. The mean age of diagnosis was 14.9 $\pm$ 1.5 years, and there was no gender predominance. Family history of NERD was present in 2 patients (patients 2 and 10). Half of the patients had exposure to passive cigarette smoke at home. Baseline demographic and laboratory characteristics of all patients were given in Table 2. All patients except patient number 9 had reversible wheezing attacks treated by bronchodilators in our clinic. Patient number 9 had no symptoms of asthma at the time of admission but had borderline bronchial hyperreactivity with metha-

choline. Clinical characteristics, diagnostic tests, and follow-up of each patient are shown in Table 3.

Polypectomy was performed in 2 patients in another center 3 years before their diagnosis (patients 1 and 2) (Table 3). These 2 patients had increased serum eosinophil counts (820/mL and 1000/mL, respectively). CRS with nasal polyps was present in only patient 1 at the time of diagnosis. This patient had intermittent partial anosmia and apparent nasal polyps in routine anterior rhinoscopy. There was accompanying atopic disease in 6 patients (Table 3). Patients who had allergic rhinitis were all sensitized to house dust mite, 4 of whom were also sensitized to pollens and animal dander (patients 3, 6, 7, and 10).

Culprit NSAIDs in history and results of OPTs

The most frequently defined NSAIDs for the reactions were naproxen and flurbiprofen. Aspirin was the culprit drug in only 1 patient (patient 10). Hypersensitivity to at least 2 different NSAIDs was demonstrated with OPT in each patient. Details of symptoms and signs during OPT are given in Table 3. Nimesulide was determined as a safe alternative for patients 2, 3, 4, 5, 7, 8, 9, and 10, and meloxicam for patients 1 and 6.

Follow-up

The mean duration of follow-up after diagnosis of NERD was 28.9 $\pm$ 12.4 months. All patients were recommended to strictly avoid the offending NSAID during the follow-up. They were informed about their disease and were provided a written list of NSAIDs that they could not use and the safe alternatives that they could use. Patient 9 has been under follow-up for the past year and he is asymptomatic in terms of asthma. The asthma control level of other patients was well-controlled (Table 3). There were no hospitalizations, ED visits or use of systemic corticosteroids for asthma in any of the patients during follow-up. During follow-up, no patients developed acute recurrent sinusitis/CRS with or without nasal polyps except the first 2 patients. Aspirin desensitization was required in these 2 patients with recurrent nasal polyps. Both of these patients had their first polypectomies before their admission to our clinic. Polypectomy was performed for the second time on patient 1, which was accompanied with aspirin desensitization just after surgery. Currently, this patient has been taking 300 mg/day aspirin and had sinusitis only once a year under desensitization compared to 4 to 5 times per year with systemic corticosteroid courses for polyps 2 to 3 times/year before desensitization. The other patient with a previous polypectomy (patient 2) developed CRS with polyps and had intermittent partial anosmia. This patient has been using continuous nasal corticosteroid treatment for the last 2 years and required a systemic corticosteroid course 2 times/year for upper respiratory tract disease but was asymptomatic with respect to asthma without an asthma prophylactic treatment. She was also recommended a polypectomy followed by aspirin desensitization but did not agree.

TABLE 3. Clinical characteristics, diagnostics, and follow-up of adolescents with NERD

Patient number. Age (years)/sex	Underlying respiratory diseases (asthma severity at diagnosis)	Comorbid atopic disease	OPTs with NSAIDs and the reactions		Current asthma treatment	Follow-up	
						Asthma control	Upper airway symptoms
1. 16/F	CRS with nasal polyp, asthma (mild persistent)	No	Flurbiprofen	Rhinorrhea, dyspnea, wheezing, 57% ↓FEV ₁ , hives, angioedema, hypotension	640 µg BUD+LABA	Well controlled	No (under aspirin desensitization + use of LTRA+nasal steroid)
			Nimesulide	Dyspnea, wheezing, 40% ↓FEV ₁ , hives, angioedema			
2. 14/F	CRS with nasal polyp, asthma (mild persistent)	No	Naproxen	Nasal congestion, rhinorrhea, sneezing chest tightness, dyspnea, flushing	SABA as needed	Well controlled	Yes (CRS with nasal polyp, partial intermittent anosmia, use of nasal steroid)
			Diclofenac	Nasal congestion, rhinorrhea, chest tightness, dyspnea, flushing			
3. 13/F	Asthma (mild persistent)	Allergic rhinitis	Ibuprofen	Nasal congestion, rhinorrhea, hives, angioedema	320 µg BUD+LABA	Well controlled	No
			Naproxen	Nasal congestion, rhinorrhea, hives, angioedema			
4. 15/F	Asthma (mild persistent)	Atopic eczema	Flurbiprofen	Nasal congestion, coughing, angioedema	160 µg BUD+LABA	Well controlled	No
			Naproxen	Nasal congestion, coughing, angioedema			
5. 14/F	Asthma (mild persistent)	No	Aspirin ^a	Rhinorrhea, nasal congestion, sneezing, angioedema	160 µg BUD+LABA	Well controlled	No
6. 16/M	Asthma (moderate persistent)	Allergic rhinitis	Naproxen	Rhinorrhea, dyspnea, wheezing, coughing, 27.7% ↓FEV ₁ , hives, angioedema	200 µg BUD	Well controlled	No
			Ibuprofen	Rhinorrhea, dyspnea, wheezing, 16% ↓FEV ₁ , flushing, angioedema			

(Continued)

TABLE 3. Continued

Patient number. Age (years)/sex	Underlying respiratory diseases (asthma severity at diagnosis)	Comorbid atopic disease	OPTs with NSAIDs and the reactions	Current asthma treatment	Follow-up	
					Asthma control	Upper airway symptoms
7. 13/M	Asthma (mild persistent)	Allergic rhinitis	Ibuprofen Rhinorrhea, dyspnea, coughing, wheezing, 28% ↓ FEV ₁ , angioedema	SABA as needed	Well controlled	No
			Metamizole Dyspnea, coughing, wheezing, 30% ↓ FEV ₁ , angioedema, hives			
8. 14/M	Asthma (mild persistent)	Allergic rhinitis	Naproxen Rhinorrhea, nasal congestion, sneezing dyspnea, wheezing, 23% ↓ FEV ₁ , angioedema	320 µg BUD	Well controlled	No
			Flurbiprofen Rhinorrhea, nasal congestion, sneezing dyspnea, wheezing, 25% ↓ FEV ₁ , angioedema			
9. 17/M	No ^b	No	Flurbiprofen Nasal congestion, rhinorrhea, conjunctival injection, chest tightness, angioedema	No treatment	Asymptomatic	No
			Aspirin ^b Nasal congestion, rhinorrhea, chest tightness, angioedema			
10. 17/M	Asthma(mild persistent)	Allergic rhinitis	Naproxen Nasal congestion, rhinorrhea, dyspnea, coughing, wheezing, 26% ↓ FEV ₁ , hives, angioedema, flushing	160 µg BUD+LABA	Well controlled	No
			Aspirin Nasal congestion, rhinorrhea, dyspnea, coughing, wheezing, 30% ↓ FEV ₁ , hives, angioedema, flushing			

^aThe patient who described reactions with flurbiprofen and diclofenac could not be tested with both of them separately because the patient could not stay more than a day; therefore, OPT was performed only with aspirin.

^bBronchial hyperreactivity to methacholine of this patient was borderline (PC₂₀FEV₁ = 5.86 mg/mL). This patient gave a history of reaction only with flurbiprofen. Aspirin challenge was performed to demonstrate cross-reactivity.

BUD = budesonide; CRS = chronic rhinosinusitis; F = female; FEV₁ = forced expiratory volume in 1 second; LABA = long-acting bronchodilator; LTRA = leukotriene receptor antagonists; M = male; NERD = NSAIDs-exacerbated respiratory disease; OPT = oral provocation test; PC₂₀FEV₁ = Provocative concentration of methacoline required to decrease FEV₁ by 20%; SABA = short-acting bronchodilator.

Discussion

This is the first retrospective observational case study that evaluated NERD solely in adolescents. So far, no published study assessed either short-term or long-term follow-up in NERD in this age group. The mean follow-up period of the patients in this observational study was more than 2 years after the diagnosis. We observed that NERD in childhood has more differences than similarities to NERD in adults. First, progression of the disease in childhood is different from the usual clinical course in adulthood. Second, the asthma component is not severe. Third, unusual findings such as hives or angioedema frequently accompany usual findings induced by NSAIDs in pediatric NERD cases. Rhinologists may encounter these children as CRS with or without nasal polyps associated with asthma or asthma-like symptoms in their daily practice.

Aspirin-exacerbating respiratory disease or NERD typically presents with persistent upper respiratory tract complaints within the third decade of the lifespan. These patients generally experience rhinitis symptoms followed by anosmia. Most of them are treated several times by head and neck specialists for sinus disease at first. Then most of them undergo sinus/polyp surgery early in the course of their disease.⁹ Thereafter, it has a progressive course; asthma symptoms start to appear within 2 years, which are usually followed by development of NSAID hypersensitivity.¹⁵ Although CRS has been the starting point for diagnosis in adults,¹⁶ all but 1 adolescents included in the present study initially had symptoms and/or findings associated with asthma. All these patients had either doctor diagnosis of asthma or had repeated prescriptions with anti-asthma medications before their chronic upper respiratory tract complaints. Hypersensitivity to NSAID subsequently developed after an interval of 5 years from the initial asthmatic complaints. Nasal endoscopy was performed in all patients at the time of diagnosis, even if they were asymptomatic, and they were regularly followed with respect to upper respiratory tract findings. Based on these findings, we cannot clarify why NERD has a different course in children. However, we believe that longer observation periods can reflect the course more clearly.

Another prominent finding of our study was the severity of asthma in our patients. Adolescents with NERD in our study did not have severe or difficult-to-treat asthma. This was contrary to the reports in the adult studies in which 2 out of 3 adult patients with NERD had severe asthma, and half of them use chronic oral corticosteroids for asthma control.^{3,4,15} In our case series, 5 patients are on combination treatment with inhaled corticosteroid (ICS) plus long-acting bronchodilator (LABA) (160–640 µg/day budesonide [BUD]+LABA), 2 patients are on ICS treatment (200–400 µg/day BUD), 2 patients are on inhaled short-acting bronchodilator (SABA) treatment as needed. However, none of them had an exacerbation treated with systemic corticosteroid in the last year. In addition, inhaler corticosteroid prophylaxis of 2 patients was switched to

SABA as needed because their asthma was well controlled during follow-up. Certainly, the difference in asthma severity and course between adults and adolescents with NERD may be related to the severity of upper respiratory tract disease.^{17,18} In the published studies, two-thirds of adult patients with NERD had severe asthma and CRS with or without nasal polyps.^{4,15} In our case series, only 2 patients had CRS with nasal polyps. Interestingly, 1 of them needed high-dose ICS+LABA whereas the other needed only as-needed SABA for control of asthma. Therefore, there may be differences between the patients considering the course of the disease. On the other hand, in the study performed by Bochenek et al.,⁴ adult patients diagnosed with aspirin-exacerbated respiratory disease were separated to 4 sub-phenotypes by latent class analysis. According to this, class 1 patients had moderate-course asthma, intensive upper airway symptoms, and blood eosinophils, whereas class 2 patients had mild-course asthma. Patients in classes 3 and 4 had very poorly controlled asthma. Our patients seem to carry clinical characteristics of class 1 or 2. Certainly, the diseases course may change over time in inflammatory diseases. Almost half of the patients in class 4 in Bochenek et al.'s study⁴ with very poorly controlled asthma had childhood-onset asthma. Perhaps, our patients who do not seem to have severe asthma may progress to poorly controlled asthma and CRS in time.

In general, hypersensitivity to NSAIDs presents with urticaria and/or angioedema in childhood.¹⁹ Urticaria and/or angioedema also develop in adults with hypersensitivity to NSAIDs, usually accompanying chronic urticaria.²⁰ However, reactions that arise with aspirin or other NSAIDs in NERD are generally encountered as isolated naso-ocular reactions with/without lower respiratory tract symptoms/signs.⁹ Symptoms such as hives, angioedema, flushing, gastric pain, and hypotension were defined as non-classical and accepted as unusual in adults with NERD.⁹ Unlike adults, all of the adolescents with NERD included in the present study had nonclassical signs together with naso-ocular and/or lower airway symptoms. At the moment we do not know why the cutaneous signs are more frequently observed in adolescents with NERD than adults. However, in a recent review reporting about advanced phenotyping in hypersensitivity to NSAIDs, some patients with hypersensitivity to NSAIDs were described to have “blended reactions,” with respiratory symptoms together with cutaneous and gastrointestinal symptoms.²¹ Perhaps these patients are in the spectrum of NERD that requires further investigation and definition.

The main limitation of our study is the limited number of patients; therefore, we cannot generalize our results to all childhood ages. On the other hand, although there is no published study reporting the prevalence of NERD in childhood, we think that it must be a very rare form of NSAID hypersensitivity considering the low frequency of aspirin sensitivity in general 2% in adolescents between 13 and 17 years old and 1% in children under 13 years old.³ Yet again, the present study represents a real-life, retrospective

observational case study including only adolescents with NERD and its primary aim is not to determine the incidence of NERD at this age group. Certainly, multicenter studies are needed not only to determine the prevalence of NERD in childhood but also to better understand the natural history and investigate the pathogenesis of this form of hypersensitivity to prevent irreversible changes in younger ages both upper and lower airways.

Conclusion

NERD has favorable clinical characteristics and course in children. Few patients in childhood refer with typical

chronic upper respiratory tract complaints. The asthma component has a mild course and seems to be well-controlled in the short-term follow-up. Most of these children may apply to ear/nose/throat (ENT) clinics; therefore, rhinologists must be aware that some children and adolescents with CRS with or without refractory polyps may have a subset of NERD and may have a very subtle (minimal asthma) presentation initially. However, further multicenter studies with longer follow-up periods are required to study the pathogenesis and develop new strategies to prevent and or treat cases in childhood in hopes of helping control the disease course in adults. 

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