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Results of nonsteroidal anti-inflammatory drug provocation tests and difficulties in the classification of children with nonsteroidal anti-inflammatory drug hypersensitivity

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in children and can frequently cause hypersensitivity reactions. Rates of confirmed NSAID hypersensitivity (NSAID-H) in children are low.

Objectives: To evaluate the results of drug provocation tests (DPTs) with NSAIDs and to evaluate the difficulties encountered in the classification of NSAID-H in children.

Methods: The study included patients with suspected NSAID-H who were examined in our clinic between January 1, 2015, and December 31, 2018. Oral provocation tests with NSAIDs were performed and reactions were classified according to the European Academy of Allergy and Clinical Immunology position paper on NSAID-H.

Results: A total of 243 patients (57.2% male patients) presented with suspected NSAID-H during the study period. Of these, 168 patients (69.1%) had a history of reaction to ibuprofen. Isolated skin involvement was the most frequent symptom (86%). A total of 238 DPTs were performed with the suspected agents and 34 had positive results. The families of 12 patients refused provocation testing with the suspected agent or aspirin and these patients could not be diagnosed. Of the 231 patients, 47 patients (20.3%) received a diagnosis of NSAID-H. Twenty patients with NSAID-H could not be classified because their guardians did not consent to further testing with aspirin.

Conclusion: Performing diagnostic tests is important in patients with no contraindications. Characterizing these reactions in children can be difficult because of the coexistence of indistinguishable symptoms in their history and DPTs, as well as the need for multiple provocation tests. Therefore, further research is needed on this subject.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common causes of drug hypersensitivity reactions.^{1,2} The reported prevalence of NSAID hypersensitivity (NSAID-H) is between 0.6% and 5.7% in the general population³ and 0.3% in children. Five

percent of children with asthma had a positive aspirin challenge result^{2,4} and 0.9% of 976 children with asthma were reported to have confirmed NSAID-H.⁵ Paracetamol and ibuprofen are the most commonly reported culprit agents in the pediatric population.⁶

Because NSAIDs are often used in the treatment of fever, eruptions suspected to be NSAID-H may be caused by an underlying acute febrile illness. The rates of NSAID-H diagnosis as low as 16.9% to 27% have been reported in children.^{7–10} Therefore, a diagnosis of NSAID-H should not be made in children before completing diagnostic tests if their condition is nonrecurrent and/or nonsevere and/or if they have been using multiple NSAIDs.¹¹

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There are 2 main pathologic mechanisms of NSAID-H. Patients who have reactions to more than 1 class of NSAIDs are classified as cross-intolerant, which is most commonly due to cyclooxygenase 1 inhibition. Other patients react to only 1 group of NSAIDs and are called selective responders, which is generally a result of immunologic mechanisms.^{11,12} Classification of NSAID reactions is based on these mechanisms and the presence of underlying disease, but some reactions can be difficult to classify.^{9,13,14} In 2018, the European Academy of Allergy and Clinical Immunology (EAACI) Task Force proposed a new classification for children, dividing them into age groups older than and younger than 10 years.¹¹ In this study, we aimed to evaluate the features of NSAID-H clinical presentation in children using the new classification and identify difficulties in applying this classification.

Methods

This study included patients who presented with suspected NSAID-H and were examined in our pediatric allergy clinic between January 1, 2015, and December 31, 2018. The local ethics committee approved the study design and protocols.

A detailed history was taken, including the spectrum and timing of symptoms, dose and route of administration, concomitant medications, history and timing of previous reactions, and previously tolerated NSAIDs, as well as previous aspirin use and any reactions. Coexisting chronic diseases were recorded, especially asthma, chronic rhinosinusitis, nasal polyps, chronic spontaneous urticaria, and family history of allergic diseases.

Patients with a history suggestive of NSAID-H were advised to undergo skin prick or intradermal tests and oral provocation tests (OPTs) with the drug (suspected drug, aspirin, or alternative) at least 1 month after the initial reaction. Use of antihistamine medications and other drugs that could affect the skin tests or drug provocation tests (DPTs) were discontinued a week before testing. Written informed consent was obtained from the patients' legal guardians. Tests were not performed on patients whose guardians did not provide consent. Patients diagnosed as having NSAID-H and their caretakers were provided written information, including a list of forbidden and alternative drugs.

Skin Prick and Intradermal Tests

Skin prick and intradermal testing was performed when the suspected drug was paracetamol.¹¹ Isotonic saline solution was used for dilution. All the drugs were initially tested on the volar forearm skin with the prick method, followed by intradermal injection of 0.02 mL of diluted drug into the volar forearm skin. Readings were taken 20 minutes after injection. Induration larger than 3 mm in diameter accompanied by erythema was considered a positive result.¹⁵

Drug Provocation Tests

The DPTs were performed to confirm hypersensitivity with the culprit drug, to confirm or exclude cross-reactivity with aspirin, and to determine a tolerated alternative drug. The European Network of Drug Allergy guidelines for DPTs were carefully respected.¹⁶

Suspect drugs were administered at divided doses every hour until a cumulative dose close to the age and weight-adjusted daily dose of the drug was reached. To avoid a false-negative challenge result, the total cumulative dose should be at least 15 to 20 mg/kg for paracetamol, 10 mg/kg for ibuprofen, and 15 to 20 mg/kg for aspirin, with the maximal dose determined for age and weight (Table 1).¹¹ The results of DPT were considered positive in the presence of any of the following objective signs and symptoms related to a hypersensitivity reaction: cutaneous symptoms (urticaria, angioedema, and/or conjunctivitis), upper or lower respiratory tract symptoms (rhinorrhea, sneezing, nasal congestion, cough, and/or dyspnea), greater than 15% decrease in forced expiratory volume in 1 second during an OPT, and cardiovascular system symptoms (change in heart rate and hypotension).¹⁷ The patients' caretakers were asked to contact the physician 24 hours after the DPT to report delayed reaction.

Aspirin Provocation Test

Aspirin provocation was performed to confirm or exclude hypersensitivity and/or cross-reactivity. Placebo capsules were administered on the first day; on the second day, 4 incremental doses were given at 1.5-hour intervals until the maximal therapeutic dose was reached (cumulative dose, 15–20 mg/kg) (Table 1).¹¹ Forced expiratory volume in 1 second was measured at the beginning of the test and at 30-minute intervals.¹⁷

Definitions and Classification of Nonsteroidal Anti-inflammatory Drugs Hypersensitivity

Patients with positive OPT results who had a history of reactions to different NSAIDs or multiple reactions to the same NSAID and those whose first reaction was severe anaphylaxis were accepted as having NSAID-H. Reactions were classified and defined according to the previous EAACI position paper¹³ and revised again according to the latest EAACI position paper on NSAID-H.¹¹ In the new classification, subgroups of cross-intolerant people are not used for children younger than 10 years. Symptoms that occur within the first 24 hours were considered immediate reactions and those that occurred later were considered delayed reactions.¹¹

Statistical Analysis

Statistical analyses were performed using SPSS statistical software, version 22 (IBM Corporation, Armonk, New York). Numbers and percentages were reported for discrete variables. Continuous variables were presented as means and SDs for normally distributed data and as medians and interquartile ranges (IQRs) for non-normally distributed data. The χ^2 test was performed to compare nonparametric data. Logistic regression analysis was performed to determine the risk factors for persistence of the disease. Parameters with values of 0.20 and below in univariate analysis were included in the multivariate analysis. The results were given as odds ratios and 95% CIs. For all analyses, $P < .05$ was considered statistically significant.

Table 1
Drug Provocation Test Protocols

Drug name	Initial dosage	Dosage interval, min	No. of steps	Maximum dose, mg/kg
Paracetamol	Between one-tenth to one-fourth of the age- and weight-adjusted therapeutic dose	60	3–4	15–20
Ibuprofen	Between one-tenth to one-fourth of the age- and weight-adjusted therapeutic dose	60	3–4	10
Aspirin	Between one-tenth to one-fourth of the age- and weight-adjusted therapeutic dose	60	3–4	15–20

Table 2

Characteristics of Patients With Diagnosis of Nonsteroidal Anti-inflammatory Drug Hypersensitivity Based on OPT

Patient no.	Age at reaction, y	Sex	Suspected agent	Presence of asthma or chronic urticaria	OPT agent	OPT result	Aspirin reaction	Classification	Alternative drug
1	>10	M	Paracetamol	No	Paracetamol	Urticaria	ND	SNIUA	Meloxicam and ibuprofen
2	>10	M	Ibuprofen, paracetamol	No	Paracetamol	Urticaria	ND	SNIUA	
					Ibuprofen	No reaction			
3	<10	F	Paracetamol	No	Paracetamol	Urticaria	ND	SNIUA	Ibuprofen
4	>10	F	Paracetamol	Asthma	Paracetamol	Urticaria	ND	SNIUA	Ibuprofen
5	>10	F	Ibuprofen	No	Ibuprofen	Angioedema	No reaction	SNIUA	Paracetamol
6	<10	M	Paracetamol	No	Paracetamol	Urticaria	ND	SNIUA	Ibuprofen
7	<10	M	Ibuprofen	Asthma	Ibuprofen	Angioedema	No reaction	SNIUA	Paracetamol
8	<10	F	Ibuprofen	No	Ibuprofen	Angioedema	No reaction	SNIUA	Paracetamol
9	>10	M	Flurbiprofen, metamizole	No		Skin reaction		NIUA	Paracetamol and meloxicam
10	>10	F	Ibuprofen	Asthma	Ibuprofen	Angioedema	Nasal congestion, angioedema	NERD/blended	Paracetamol
11	>10	F	Ibuprofen	Asthma	Ibuprofen	Angioedema	Angioedema and respiratory distress (20% decrease in FEV ₁)	NERD/blended	Paracetamol
12	>10	F	Ibuprofen	Asthma	Ibuprofen	Urticaria and respiratory distress	Urticaria and respiratory distress	NERD/blended	Meloxicam
13	>10	M	Ibuprofen, paracetamol	Asthma	Ibuprofen	Angioedema and respiratory distress (16% decrease in FEV ₁)	Angioedema	NERD/blended	Paracetamol
					Paracetamol	No reaction			
14	>10	F	Paracetamol	No	Paracetamol	Fixed drug eruption	ND	Fixed drug eruption	Ibuprofen
15	>10	F	Paracetamol	Asthma	Paracetamol	Urticaria	ND	SNIUA	Ibuprofen
16	>10	F	Aspirin	Asthma	Paracetamol	Respiratory distress (30% decrease in FEV ₁)	ND	NERD	
					Meloxicam	Respiratory symptoms (25% decrease in FEV ₁)			
17	>10	M	Ibuprofen	Asthma	Ibuprofen	Respiratory distress (27% decrease in FEV ₁)	ND	NERD	Paracetamol
18	<10	M	Ibuprofen	Asthma	Ibuprofen	Urticaria, respiratory distress	ND	CI	Paracetamol
19	>10	F	Ibuprofen, paracetamol	Asthma	Ibuprofen	Angioedema and respiratory distress	ND	NERD/blended	Meloxicam
					Paracetamol	No reaction			
20	<10	M	Ibuprofen	Asthma and chronic urticaria	Ibuprofen	Angioedema and respiratory distress	ND	CI	Paracetamol
21	>10	M	Dexketoprofen, ibuprofen	Chronic urticaria	Ibuprofen	Urticaria	ND	NECD	Meloxicam
22	<10	M	Ibuprofen	No	Ibuprofen	Urticaria and angioedema	Urticaria with placebo	Unknown	Paracetamol
23	>10	F	Ibuprofen	No	Ibuprofen	Angioedema	ND	Unknown	Paracetamol
24	<10	M	Ibuprofen, paracetamol	No	Ibuprofen	Angioedema	ND	Unknown	Paracetamol
					Paracetamol	No reaction			
25	>10	M	Ibuprofen	No	Ibuprofen	Angioedema	ND	Unknown	Paracetamol
26	<10	M	Ibuprofen	No	Ibuprofen	Angioedema	ND	Unknown	Paracetamol
27	>10	F	Flurbiprofen	No	Flurbiprofen	Angioedema	ND	Unknown	Paracetamol
28	>10	F	Ibuprofen	No	Ibuprofen	Angioedema	ND	Unknown	Paracetamol
29	<10	F	Ibuprofen	No	Ibuprofen	Angioedema	ND	Unknown	Unknown
30	<10	F	Ibuprofen	No	Ibuprofen	Angioedema	ND	Unknown	Unknown
31	<10	F	Ibuprofen	Asthma	Ibuprofen	Angioedema	ND	Unknown	Paracetamol is used at home
32	<10	M	Ibuprofen, paracetamol	No	Ibuprofen	Urticaria	ND	Unknown	Paracetamol
					Paracetamol	No reaction			
33	<10	F	Ibuprofen	No	Ibuprofen	Angioedema	ND	Unknown	Paracetamol is used at home
34	>10	F	Acetyl salicylic acid, ibuprofen	No	Ibuprofen	Urticaria and angioedema	ND	Unknown	Meloxicam
35	>10	F	Ibuprofen	No	Ibuprofen	Urticaria and angioedema	ND	Unknown	Meloxicam
36	<10	M	Ibuprofen	No	Ibuprofen	Angioedema	ND	Unknown	Paracetamol is used at home

Abbreviations: CI, cross-intolerance; FEV₁, forced expiratory volume in 1 second; ND, not done; NECD, nonsteroidal anti-inflammatory drug–exacerbated cutaneous disease; NERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease; NIUA, nonsteroidal anti-inflammatory drug–induced urticaria/angioedema; OPT, oral provocation test; SNIUA, single nonsteroidal anti-inflammatory drug–induced urticaria/angioedema.

Results

The study included 243 patients; 139 (57.2%) were male. The median age was 84.3 (IQR, 50.7–139.2) months. The median time between index reaction and diagnostic evaluation was 2.54 (IQR, 1.4–7.7) months. The study group included 158 patients (65%) younger than 10 years. History included immediate reaction in 226 patients, delayed reaction in 16 patients, and unknown reaction time in 1 patient. Reactions were reported with ibuprofen in 168 patients (69.1%) and with paracetamol in 90 patients (37.0%). Reaction to 1 NSAID group was reported in 197 patients, to 2 different groups in 42 patients, and to 3 different groups in 2 patients. Isolated skin involvement (urticaria, maculopapular exanthema, angioedema, and/or itching) was the most frequent symptom (86%). A total of 238 DPTs were performed with the suspected agents and 34 had positive results. Thirty-nine DPTs were performed to identify an alternative agent. The DPTs with aspirin were performed for 16 patients with 2 as the suspected agent.

The results of skin tests performed on 11 patients with suspected paracetamol sensitivity were negative. Of the 243 patients, 231 patients or their caretakers consented to DPTs for a NSAID-H diagnosis. However, in this group, 11 patients or their caretakers did not consent to DPTs with the suspected agent. The patients were diagnosed based on clinical history. Six patients had a history of anaphylaxis, 1 patient had angioedema with dextketoprofen and asthma, 1 had angioedema with ibuprofen, 1 patient had urticaria with aspirin on multiple occasions, 1 patient had angioedema with ibuprofen and metamizole, and 1 patient had urticaria and angioedema with aspirin and flurbiprofen. These patients or their caretakers did not consent to a provocation test with these suspected agents. Four patients were younger than 10 years, and 7 patients were older than 10 years.

NSAID-H diagnosis was confirmed by DPTs in 36 of 220 patients (16.3%) tested with the suspected agent. Of these patients, 34 had positive results on DPTs with the suspected agents. One patient had a history of reaction to aspirin and had positive DPT results with paracetamol and meloxicam as alternative agents. One patient had a history of reaction to flurbiprofen and metamizole and the results of a DPT with aspirin were positive. The characteristics of these

patients are summarized in Table 2. In addition, NSAID-H diagnosis was confirmed by DPTs in 21 of 69 patients (30.4%) older than 10 years and in 15 (9.93%) of 151 patients younger than 10 years at the time of the reaction ($P < .001$).

In total, we identified NSAID-H in 47 of 231 patients (30.4%) (Fig 1). NSAID-H diagnoses were made in 28 of the 76 patients (36.8%) older than 10 years and 19 of the 155 patients (12.2%) younger than 10 years at the time of the reaction. In the NSAID-H diagnosed group, 34% had comorbid asthma, and 8.5% had chronic urticaria. The most common proven reactions were to ibuprofen in 31 patients (65.95%) and paracetamol in 11 patients (23.40%). Characteristics of the reactions in the NSAID-H group are presented in Table 3.

Classification

Of the 47 patients diagnosed with NSAID-H, 27 could be classified. A total of 16 patients (59.2%) were classified as cross-intolerant and 11 (40.7%) as selective responders (Fig 1). Twenty-one of these patients, whose diagnoses were proven with DPTs, were in the older-than-10-years group and 7 of them were classified as cross-intolerant. Two patients had isolated respiratory symptoms, and 5 had both skin and respiratory symptoms during DPTs and comorbid asthma. We classified 5 patients who had mixed reactions into the blended group and 2 patients who had isolated respiratory symptoms into the NSAID-exacerbated respiratory disease (NERD) classification. In addition, 1 of these patients had nasal polyps.

Predictors of Nonsteroidal Anti-inflammatory Drugs-Hypersensitivity Diagnosis

In the univariate logistic regression analysis of patients with OPT-confirmed NSAID-H, angioedema history, sex, and age were associated with diagnosis. In the multivariate logistic regression model, angioedema and age were independent risk factors and main predictors of NSAID-H diagnosis (Table 4).

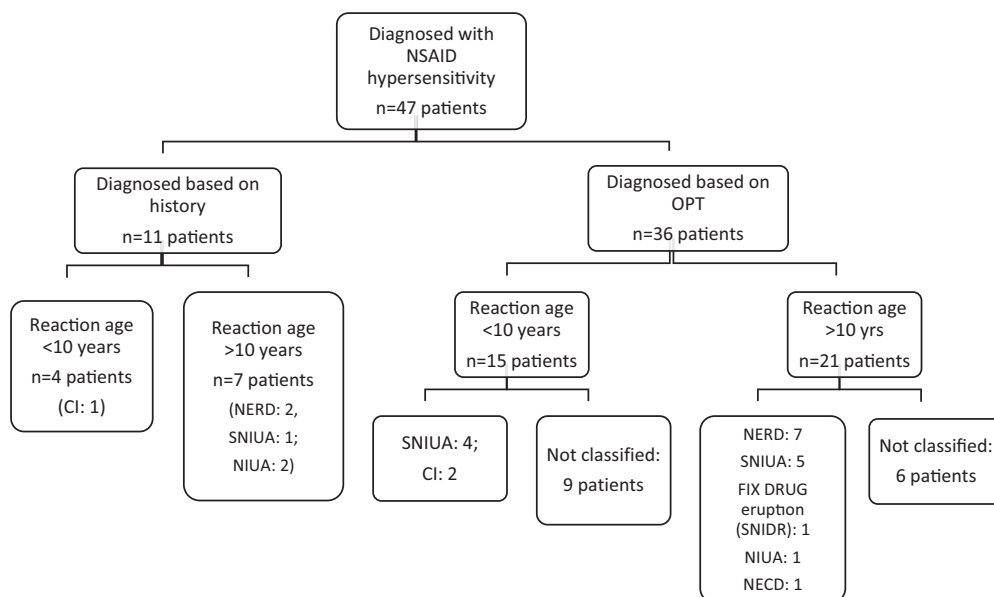


Figure 1. Classification of the diagnosed patients. CI, cross-intolerance; NECD, nonsteroidal anti-inflammatory drug–exacerbated cutaneous disease; NERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease; NIUA, nonsteroidal anti-inflammatory drug–induced urticaria/angioedema; NSAID, nonsteroidal anti-inflammatory drug; OPT, oral provocation test; SNIDR, single nonsteroidal anti-inflammatory drug–induced delayed reaction; SNIUA, single nonsteroidal anti-inflammatory drug–induced urticaria/angioedema.

Table 3
Characteristics of the NSAID-Hypersensitive and NSAID-Tolerant Groups

Characteristic	No. (%) of NSAID-tolerant patients (n = 184 [79.6%])	No. (%) of NSAID-hypersensitive patients (n = 47 [20.3%])	P value
Sex			.02
Male	113 (61.4)	20 (42.5)	
Female	71 (38.5)	27 (57.4)	
Age groups, y			<.001
<10	136 (73.91)	19 (40.4)	
>10	48 (26.08)	28 (59.57)	
Suspected agent			
Ibuprofen	123 (66.8)	31 (65.95)	
Paracetamol	72 (39.1)	11 (23.4)	
Flurbiprofen	1 (0.54)	6 (12.7)	
Acetylsalicylic acid	2 (1.08)	4 (8.5)	
Dexketoprofen	2 (1.08)	1 (2.12)	
Metamizole		2 (4.25)	
Naproxen	2 (1.08)		
Etodolac	1 (0.54)		
Presenting symptoms			
Angioedema	79 (42.9)	30 (63.8)	.01
Anaphylaxis	16 (8.69)	11 (23.4)	.006

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

Discussion

In this study of 243 patients with a history of suspected NSAID-H, most patients (86%) reported isolated skin symptoms, and the most commonly suspected agent was ibuprofen (69.1%). According to the history and diagnostic tests of 231 children with suspected reactions, 47 patients (20.3%) were diagnosed as having NSAID-H (11 patients were diagnosed based on presenting history and 36 patients based on OPT results).

Because NSAIDs are often used in the treatment of fever, eruptions suspected to be NSAID-H may be caused by an underlying acute febrile illness, which has been reported at rates of 16.9% to 27% in previous studies.^{7–10} The most commonly involved tissue in this study was the skin, consistent with the literature.^{1,9,10} Angioedema as a skin symptom was more frequent among children with confirmed NSAID-H diagnosis. Cavkaytar et al¹⁰ also reported that angioedema was more frequent in the NSAID-H group when compared with the NSAID-tolerant group. Although previous studies indicated that NSAID-H frequency was lower among younger children,^{18,19} Arikoglu et al¹⁴ observed no significant association between diagnosis and sex or age. In addition, NSAID-H diagnosis was confirmed in all their patients who presented with anaphylaxis.¹⁴ In our study, history of anaphylaxis, female sex, and age older than 10 years were more frequent among patients who were diagnosed as having NSAID-H. In addition, in the multivariate logistic regression model with OPT-confirmed NSAID-H, angioedema and age were independent risk factors and main predictors of NSAID-H diagnosis.

The most common causative agents of NSAID-H in children are ibuprofen and paracetamol.^{1,8–10,14} Guvenir et al⁸ reported that paracetamol was the most common suspected drug in NSAID-H (40.5%), but the drug most frequently associated with proven hypersensitivity reaction was ibuprofen (50%). Arikoglu et al¹⁴ reported that ibuprofen (63.8%) and paracetamol (59%) were the most frequently reported suspected drugs in patients' reaction history and 66.6% of confirmed cases of NSAID-H were to ibuprofen and 18.18% were to paracetamol. In accordance with these previous studies, the most common suspected agents in our study were ibuprofen and paracetamol (69.1% and 37.03%, respectively) and the

most frequently proven hypersensitivity reactions were also to ibuprofen and paracetamol (65.95% and 23.40%, respectively).

NSAID-H reactions may be IgE mediated (selective responders group) or due to cyclooxygenase inhibition (cross-intolerant group). The latest guideline states that cross-intolerant reactions are more common and selective allergic reactions are less common in children than adults, although regional variations may be observed.¹¹ Consistent with these data, cross-intolerant reactions were more common in our study, representing 16 of the 27 patients with classified conditions (59.2%).

In the new NSAID-H classification, children are grouped as younger and older than 10 years. Younger patients are classified as cross-intolerant or selective responders, whereas cross-intolerant subgroups are defined for older patients. When our patients were grouped accordingly, we found that patients younger than 10 years were less frequently diagnosed as having NSAID-H. In our study, 19 patients with confirmed NSAID-H were younger than 10 years (7 classified: 3 cross-intolerant and 4 selective responders). Of our patients older than 10 years, 28 had confirmed NSAID-H (20 classified: 13 cross-intolerant and 7 selective responders). Cross-intolerance was more frequent in the older age group (65%). Although it seems that cross-intolerance was less frequent for patients younger than 10 years, 12 of 19 patients could not be tested with aspirin and thus could not be classified.

The EAACI position paper reported that NERD is less common in the pediatric population.¹¹ However, in our study, the most common type of cross-intolerant reaction was NERD. Blanca-Lopez et al²⁰ reported that of 30 patients, 83% were classified as cross-intolerant and 56.6% had NSAID-induced urticaria and/or angioedema. However, their study included children younger than 14 years, whereas our study included children aged up to 18 years. The proportion of patients with confirmed NSAID-H was higher among children older than 10 years in our study and NERD classification was used only for children older than 10 years because of the most recent classification. Moreover, NERD may be more frequent among older patients, and frequencies may vary according to geographic differences.

Although the most common classification was NERD in our study group, most of the patients with underlying asthma and respiratory symptoms as the leading presentation had accompanying skin symptoms during OPTs, which may have caused confusion in classification. Although rare, skin signs and angioedema have been reported in adults with NERD.²¹ Similarly, Karagol et al²² reported that all adolescents with NERD in their study had nonclassical signs, such as angioedema, flushing, gastric pain, and hypotension with respiratory symptoms and suggested they should be described as “blended.” In their review, Cavkaytar et al²³ reported that authors have difficulty in classification of cross-intolerant pediatric patients because clinical manifestations did not correlate with underlying diseases; particularly, no patient could strictly correspond to the NERD group. Recently, Dona et al²⁴ drew attention to the patients who had both respiratory and skin symptoms with or without other systemic manifestations and suggested classifying them as a “blended” group separate from

Table 4
Predictors of NSAID-H Diagnosis With OPT

Predictor	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (female)	0.562 (0.271–1.153)	.12	0.513 (0.238–1.108)	.09
Age (>10 y)	3.967 (1.893–8.312)	<.001	3.890 (1.808–8.372)	.001
Angioedema	3.390 (1.545–7.440)	.002	3.399 (1.500–7.702)	.003
Anaphylaxis	1.297 (0.407–4.133)	.66		

Abbreviations: CI, confidence interval; NSAID-H, nonsteroidal anti-inflammatory drug hypersensitivity; OPT, oral provocation test; OR, odds ratio.

NERD and NSAID-induced urticaria and/or angioedema. Our patients had underlying asthma and respiratory symptoms as the leading presentation; we have classified them as having NERD, but we also defined them as blended under the NERD group.

In Turkey, only paracetamol and ibuprofen preparations are available in children younger than 12 years. For children, it is difficult to perform multiple DPTs and the rare prescription of aspirin for children makes the addition of aspirin DPTs to allergy workup more challenging. In our clinic, we generally prefer OPTs with the suspected agent instead of OPTs with aspirin because of the low hypersensitivity confirmation rates in the pediatric population. In our practice, we observed that patients' families are anxious about possible reactions and do not want the patients to undergo a new OPT with aspirin or with a high-risk agent, which makes it difficult to classify children as cross-intolerant or selective responders. In a study by Cousin et al.,⁹ 43 patients (40.2%) could not be classified according to the European Network for Drug Allergy 2013 classification. In another Turkish study of 106 patients, 24% were not classified.¹⁴ Similarly, we were unable to classify 12 patients younger than 10 years and 8 patients older than 10 years (42.5%), mainly because of our inability to perform aspirin provocation in all patients. In contrast, Blanca-Lopez et al.²⁰ tested their patients with aspirin first, proceeding to provocation with the suspected drug as a second step if there was no reaction to aspirin. However, this 2-step approach may be useful for patients in the older-than-10-years group. Simsek et al.²⁵ also reported that performing OPTs with aspirin first may result in much lower numbers of OPTs for NSAID-H diagnosis and the patients' caretakers may feel more confident when providing consent.

Although NSAID-H is frequently suspected during childhood, the rate of approval with allergy workup is low, especially in children younger than 10 years. It is important to distinguish whether suspected reactions in children are due to medication or illness. Standard approaches and diagnostic tests are required for diagnosis. Classification of children can be difficult because of the necessity of multiple provocation tests, especially because of the need for provocation with aspirin. Furthermore, accompanying skin and respiratory symptoms are common in children, which causes confusion in classification. Further studies to identify blended reactions in children are needed.

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