ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2025.891
Asthma Allergy Immunol 2025;23:1-9

RESEARCH ARTICLE

Received: 24.06.2025 • Accepted: 18.09.2025
Online Published: 19.11.2025

Real-World Evaluation of NSAID Hypersensitivity in Children: Diagnostic Challenges and Risk Factors

Merve KARACA SAHIN, Muhammed Fatih ERBAY, Nilay CALISKAN, Guler YILDIRIM, Hamit BOLOGUR, Hilal GUNGOR, Sefika Ilknur KOKCU KARADAG, Deniz OZCEKER

The University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital, Department of Pediatric Allergy and Immunology, Istanbul, Türkiye

Corresponding Author: Merve Karaca Sahin ✉ karacasahinmerve@gmail.com

ABSTRACT

Objective: Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in children for their antipyretic and analgesic effects, but they are frequently associated with hypersensitivity reactions. The aim of this study is to describe the clinical features, diagnostic process, and risk factors associated with NSAID hypersensitivity (NSAID-H) in children and to highlight the challenges in its classification and management.

Materials and Methods: Between 2017 and 2023, children referred to our clinic with a history of reaction to any NSAIDs were retrospectively evaluated. Reactions were classified according to the European Academy of Allergy and Clinical Immunology position paper on NSAID hypersensitivity.

Results: Of the 93 patients evaluated for NSAID-H, the median age of symptom onset was 6 years (ranging from 6 months to 17 years and 5 months). Eighty-six patients underwent a drug provocation test, of whom 18 (24%) had positive reactions, while 7 diagnoses were based on clinician-documented anaphylaxis. NSAID-H was confirmed in 25 children (27%). Ibuprofen was the most frequent culprit, followed by paracetamol. Importantly, off-label NSAID use was reported in 11% of the patients. Paracetamol and nimesulide were tolerated in 95% and 63% of alternative challenges, respectively. Four children were classified as selective reactors to paracetamol, and four were classified as cross-intolerants while the remaining patients could not be classified. Risk of NSAID-H increased with age > 10 years, multiple previous reactions, reaction onset < 1 h, angioedema/anaphylaxis, co-existing allergy, and a family history of drug allergy.

Conclusion: Drug provocation testing for diagnosing NSAID-H and should be performed in all cases, unless there is a contraindication. However, in the pediatric population, parental concerns regarding drug provocation testing, frequent off-label use of NSAIDs, and the presence of patients whose reactions do not fully fit the NSAID-H classification create challenges in diagnosis and management.

Keywords: Children, hypersensitivity, ibuprofen, nonsteroidal anti-inflammatory drugs, paracetamol

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly preferred in children due to their antipyretic and analgesic effects. NSAIDs are notably the most commonly encountered drug hypersensitivity in children, and their management varies among clinicians and across countries (1-3).

Based on the onset time of the reaction, NSAID hypersensitivity can be classified into immediate-type and delayed-type reactions (4). The first is immediate reactions mediated by specific IgE antibodies, such as urticaria, angioedema, and/or anaphylaxis caused by a single NSAID (SNIUAA). Cross-intolerance reactions account for other immediate-type reactions. These reactions are elicited by multiple NSAID subclasses, with pharmacological mecha-

ORCID Merve Karaca Sahin / 0000-0001-8783-0514, Muhammed Fatih Erbay / 0000-0002-4128-3081, Nilay Caliskan / 0000-0002-5546-0034, Guler Yildirim / 0000-0001-7852-9252, Hamit Bologur / 0000-0003-1092-8833, Hilal Gungor / 0000-0003-1092-8833, Sefika Ilknur Kokcu Karadag / 0000-0001-9234-633x, Deniz Ozceker / 0000-0002-0032-6727

nisms contributing to their pathogenesis. There are three phenotypes of cross-reactive hypersensitivity reactions to NSAIDs. NSAID-exacerbated respiratory disease (NERD) manifests with symptoms such as dyspnea and/or nasal congestion/rhinorrhea primarily in patients with underlying asthma, rhinitis, or nasal polyps. NSAID-exacerbated cutaneous disease (NECD) presents with urticaria and/or angioedema symptoms in patients with a history of chronic urticaria (CU). NSAID-induced urticaria/angioedema/anaphylaxis (NIUAA) is classified as a group where symptoms of urticaria, angioedema, and anaphylaxis are observed in healthy children.

The second group consists of delayed-type hypersensitivity reactions, likely mediated by T cells, caused by a single NSAID (SNIDR). In this group, the reaction occurs within 24-48 hours after drug intake, but the duration may be shorter.

The diagnostic classification of NSAID hypersensitivity (NSAID-H) in children remains challenging due to the presence of concomitant viral infections, the lack of reliable in vivo and in vitro diagnostic methods, and the inconsistency of clinical manifestations and underlying conditions with current classifications.[4] The aim of this study is to determine the characteristics and risk factors of NSAID-H and to highlight the challenges in classification and management among children with suspected reactions to NSAIDs.

MATERIALS and METHODS

Participants

Between 2017 and 2023, patients (n = 93) under 18 years old with a history of reactions to NSAIDs, referred to the Pediatric Immunology and Allergy Clinic at the University Of Health Sciences, Prof. Cemil Tascioglu City Hospital, were retrospectively evaluated. The demographic data of patients and drug reactions were recorded according to the ENDA questionnaire (5).

Diagnostic Tests

Skin tests

Initially, a skin prick test (SPT) was performed, and if the result was negative an intradermal test (IDT) was administered. Commercially available preparations of the suspected NSAIDs, paracetamol (*Perfalgan®,* 10 mg/mL, Bristol-Myers Squibb, UK) and metamizole sodium (*Novalgine®,* 1 g/2 mL, Sanofi, France), were used. For both drugs, SPT was performed with the undiluted preparation, and IDT was conducted on the volar forearm at concentrations of 0.001 mg/mL, 0.01 mg/mL, and 0.1 mg/mL, diluted in normal saline. A positive reaction was determined when the wheal diameter exceeded 3 mm in comparison to the negative control, after 20 minutes of application. IDT was reevaluated at the 72nd hour for delayed reactions.

Drug Provocation Tests

The informed consent of the patients was obtained before the tests. The test was conducted in accordance with ENDA recommendations using the open challenge procedure (6).

The cumulative doses of paracetamol and ibuprofen were 15-20 mg/kg and 10-20 mg/kg, respectively. The first administration was usually 1/8 of the cumulative dose. The cumulative dose was administered in 3 or 4 steps, with 30-minute intervals between each.

The test was concluded and considered positive when objective findings were identified. After the drug provocation test (DPT), patients were observed for a minimum of two hours. If no reaction occurred following the DPT, it was advised to continue the medication at home for an additional two days. Due to ethical reasons, DPTs were not performed in patients with a confirmed history of anaphylaxis in their medical records.

DPTs were not performed with any NSAIDs used off-label beyond the recommended age group. Since the use of dexketoprofen is not approved for children in the current NSAID package inserts, and naproxen is only recommended for those aged 16 and above, DPTs were not performed with the culprit drug due to legal reasons. Instead, ibuprofen, which belongs to the same chemical group (arylpropionic acids), was used. If NSAID-H was confirmed, a DPT with alternative NSAIDs was performed. Patients who were cross-reactive or unclassified and had no prior history of reactions to these NSAIDs underwent DPT with the weak cyclooxygenase-1 (COX-1) inhibitor paracetamol and the partially selective COXf-2 inhibitors nimesulide and meloxicam. As nimesulide is approved for use in individuals aged ≥12 years and meloxicam for those aged ≥16 years in Turkey, these drugs were not administered to younger age groups.

Ethical Statement

Ethics Committee of the University Of Health Sciences, Prof. Cemil Tascioglu City Hospital approved the study protocol (No: 2023/267). Our study was conducted in accordance with the principles of good clinical practice based on the Helsinki Declaration. Ethics approval confirms that research studies are conducted in compliance with ethical standards and human rights, and that the rights of participants are protected.

Statistic Analysis

Statistical analysis was conducted using the SPSS 15.0 for Windows program. Descriptive statistics included counts and percentages for categorical variables, as well as mean, standard deviation, minimum, maximum, and median for numerical variables. The comparison of proportions in independent groups was performed using the chi-squared analysis. Since the comparisons of numerical variables did not satisfy the normal distribution assumption, the comparison between independent two groups was carried out using the Mann-Whitney U test. Logistic regression analysis was conducted to assess the risk effects of the variables. A statistical alpha level of $p < 0.05$ was considered as the threshold for significance, indicating statistical significance.

RESULTS

93 pediatric patients with suspected NSAID-related reactions were evaluated, with a total of 147 reactions recorded. The median onset age of symptoms among the patients was 6 years (ranging from 6 months to 17 years and 5 months). 55% of the patients (n = 51) had concomitant allergic diseases. Detailed information on patient characteristics and reported reactions is presented in Table I.

Suspected NSAIDs

Seventy patients (75%) reported reaction to a single NSAID, whereas twenty-three reported reactions to two or more different NSAIDs. The most suspected drugs causing the reactions were ibuprofen, paracetamol, and the combination of ibuprofen and paracetamol, with frequencies of 46%, 21%, and 18%, respectively. The other suspected NSAIDs were dexketoprofen (n=4), naproxen (n=3), flurbiprofen (n=2), metamizole (n=2), diclofenac (n=2), and tenoxicam (n=1). Ten patients had used NSAIDs off label, including naproxen, dexketoprofen, diclofenac, flurbiprofen, and tenoxicam.

Skin Prick Test and Intradermal Test Results

In total, 30 children with suspected reactions to paracetamol underwent SPT. One child had a positive SPT result and therefore did not proceed to IDT. The remaining 29 children with negative SPT results underwent IDT, of whom 3 had positive results, yielding a total of 4 patients with positive skin tests (SPT positive: n=1; IDT positive: n=3) and 26 with negative results. Among the negatives, all 26 underwent DPT; 25 tolerated the challenge, while 1 reacted. Of the 4 positives, the child with a positive SPT result underwent DPT and reacted; one child with IDT positivity at 1/1000 dilution had a negative DPT result,

Table I: Patient Characteristics and Clinical Presentation

	n (%)
Gender	
Male	45 (48)
Female	48 (52)
Concomitant allergic disease	
No	42 (45)
Allergic rhinitis	21 (23)
Asthma	12 (13)
Allergic rhinitis + Asthma	8 (9)
Chronic urticaria	4 (4)
Atopic dermatitis	2 (2)
Allergic rhinitis + Chronic urticaria	2 (2)
Asthma + Chronic urticaria	1 (1)
Food allergy	1 (1)
Family history of drug allergy	
No	79 (85)
Yes	14 (15)
Number of previous reactions	
1	57 (61)
2 ≤	36 (39)
Timing of the reaction	
Within first hour	73 (79)
1-24 hours	17 (18)
After 24 hours	3 (3)
Clinical presentation	
Maculopapular exanthem	9 (10)
Urticaria	34 (36)
Angioedema	25 (27)
Urticaria + angioedema	11 (12)
Anaphylaxis	14 (15)

and two children with IDT positivity at 1/1000 dilution did not undergo DPT because of a documented history of anaphylaxis. In patients with selective paracetamol hypersensitivity, 75% (n= 3) had skin tests (SPT and IDT) with paracetamol. In addition, SPT and IDT with metamizole were performed in two patients; both had negative skin test results and tolerated DPT without any reaction. All delayed readings at 72 hours were negative.

Drug Provocation Tests

Of the 86 patients who underwent DPT, 68 had negative results, while 18 (24%) tested positive. In 13 of these 18 patients, NSAID-H was confirmed through DPT with the culprit drug (ibuprofen in 11 cases and paracetamol in 2 cases). In four patients, due to the off-label status of the culprit drug for their age, DPT was performed with ibuprofen from the same chemical group as naproxen/dexketoprofen, yielding positive results. One patient with a history of recurrent angioedema declined DPT with the culprit drug (ibuprofen) and was diagnosed following a positive DPT with the alternative drug, nimesulide (Figure 1).

During the DPTs, urticaria and/or angioedema developed in 13 patients. Additionally, one patient experienced anaphylaxis with paracetamol, while anaphylaxis developed in three patients with ibuprofen.

15% of the patients (n = 14) described the presence of at least two systems (skin and mucosal findings, respiratory symptoms, and syncope). Among these patients 21% (n = 3) had their diagnosis confirmed by DPTs, while 28% (n = 4) were not considered to have NSAID-H following DPT. In most cases (11/18) of DPTs, reactions were observed within the first hour, while in other patients, the reaction time ranged from 1 to 5 hours. Among patients diagnosed with NSAID-H, the tolerance rate for paracetamol was 95% (n=19/20), whereas for nimesulide, it was 63% (n=5/8) (Table II).

NSAID hypersensitivity and classification

NSAID-H was identified in 25 patients (23%); 18 were diagnosed through DPT, while 7 had a confirmed history of anaphylaxis. The most frequent NSAID-H was observed with ibuprofen (n= 13; 52%), followed by paracetamol (n= 4; 16%).

Among patients, 4 were classified as CI, and 4 as SRs while the remaining patients could not be classified. All SRs were classified as SNIUAA to paracetamol. In CIs cases, two patients with CU were classified NECD. One patient with CU, AR and asthma, who developed angioedema during the DPT with ibuprofen and rhinoconjunctivitis with the nimesulide, was considered as NECD/NERD. According to the current classification, the patient

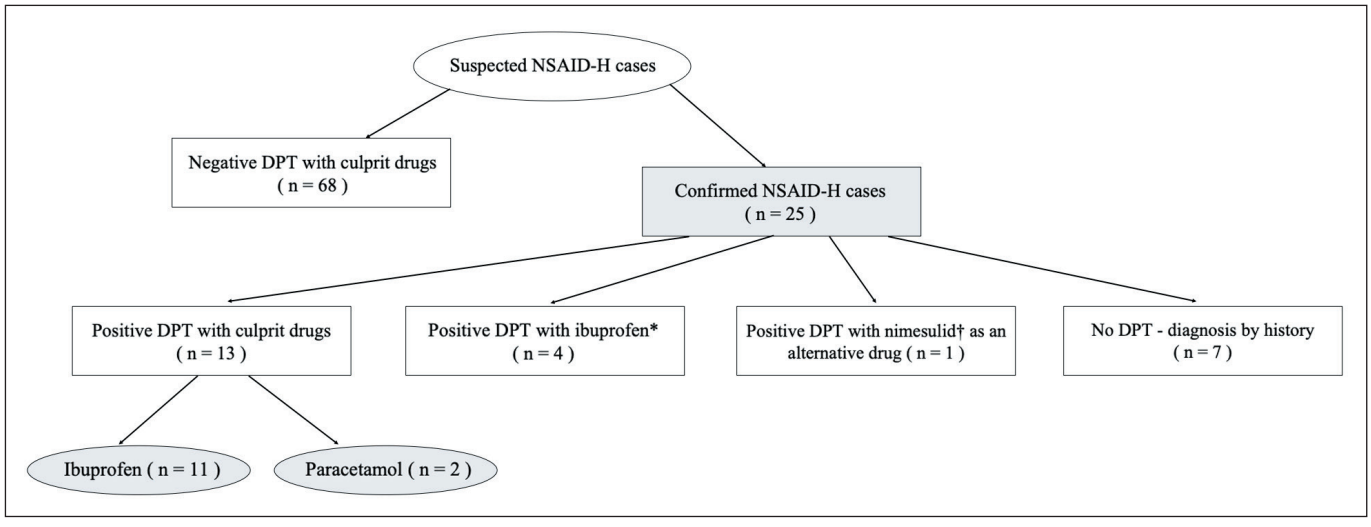

Figure 1: Diagnostic flow for suspected NSAID hypersensitivity

* Ibuprofen was selected for DPT as an age-appropriate alternative within the arylpropionic acid class, due to off-label restrictions of the suspected drugs.

† Patient had refused testing with the suspected NSAIDs (ibuprofen, diclofenac) but reacted with angioedema during DPT with the alternative drug nimesulide.

Table II: The clinical characteristics of patients with NSAID-H

Case No	Onset Age (year)	Allergy	Atopy	Presenting complaints (numbers of reactions)	Paracetamol intradermal test	DPT with culprit drug	Time to reaction during DPT (hour)	DPT with alternative drug	Type of reaction	Classification according to EAACI/ENDA Position Paper
1	7.5	CU		Ibuprofen-U	np	Ibuprofen-AO	<1	Paracetamol-NEG		NA
2	5.5	CU-AR	dp, mold	Ibuprofen-U	np	Ibuprofen-U	<1	Paracetamol-U	CI	NECD
3	4.5			Ibuprofen-U	np	Ibuprofen-U	<1	Paracetamol-NEG		NA
4	16.5	AR	df, dp, mold, pollen	Ibuprofen-AO	neg	Ibuprofen-U	4	Paracetamol-NEG Nimesulide-NEG		NA
5	16.5	CU, AR, Asthma	dp	Ibuprofen-AO	np	Ibuprofen-AO	<1	Paracetamol-NEG Nimesulide-RC	CI	NECD/NERD
6	13	AR		Ibuprofen-AO (2)	neg	Ibuprofen-ANP	<1	Paracetamol-NEG		NA
7	5	Asthma, AR	df	Ibuprofen-AO Ibuprofen-ANP	neg	Ibuprofen-ANP	<1	Paracetamol-NEG		NA
8	9	Asthma, AR		Ibuprofen-A0 (5)	np	Ibuprofen-AO	2			NA
9	15			Ibuprofen-U+AO	neg	Ibuprofen-AO	<1	Paracetamol-NEG		NA
10	16	CU	df, dp	Naproxen-AO	np	Ibuprofen -AO	5	Paracetamol-NEG Nimesulide-AO	CI	NECD
11	14.5	AR	dp, df	Naproxen-AO	neg	Ibuprofen-AO	4	Paracetamol-NEG		NA
12	15.5			Dexketoprofen-U+AO (2)	neg	Ibuprofen-AO	<1	Paracetamol-NEG Nimesulide-NEG Meloxicam-NEG		NA
13	15	AD		Ibuprofen-AO Dexketoprofen-AO	np	Ibuprofen-U+AO	<1	Paracetamol-NEG Nimesulide-NEG		NA
14	14.5			Ibuprofen-AO Dexketoprofen-AO	neg	Ibuprofen-AO	3	Paracetamol-NEG Nimesulide-NEG		NA
15	14	Asthma	dp, df pollen	Dexketoprofen-ANP Naproxen-ANP	neg	Ibuprofen-ANP	<1	Paracetamol-NEG		NA
16	6	AR		Paracetamol-U+AO	neg	Paracetamol-U	<1	Ibuprofen-NEG	SR	SNIUAA
17	3			Paracetamol-U Paracetamol-ANP	1/1000 (+)	Paracetamol-ANP	2	Ibuprofen-NEG	SR	SNIUAA
18	10	Asthm, AR	mold	Ibuprofen-AO (5) Diclofenac-AO	np			Paracetamol-NEG Nimesulide-AO	CI	NIUAA
19	5	Asthma	dp, df, mold, pollen	Paracetamol-ANP	SPT (+)			Ibuprofen-NEG	SR	SNIUAA
20	2	AR		Paracetamol-ANP	1/1000 (+)			Ibuprofen-NEG	SR	SNIUAA
21	8	Asthma	dp	Ibuprofen-AO Ibuprofen-ANP	np			Paracetamol-NEG Nimesulide-NEG		NA
22	13.5	AR		Ibuprofen-ANP Ibuprofen-AO	neg			Paracetamol-NEG		NA
23	17			Flurbiprofen-ANP	np			Paracetamol-NEG		NA
24	8.5	AR		Ibuprofen-AO Flurbiprofen-ANP	np			Paracetamol-NEG		NA
25	16.5			Tenoxicam-ANP	neg			Paracetamol-NEG		NA

AD: Atopic dermatitis, **ANP:** Anaphylaxis, **AO:** Angioedema, **AR:** Allergic rinitis, **CI:** Cross-intolerant, **CU:** Chronic urticaria, **dp-df:** Dermatophagoides pteronyssinus-dermatophagoides farinae, **DPT:** Drug provocation test, **NA:** Not applicable, **neg:** negative, **NERD:** NSAIDs-exacerbated respiratory disease, **NECD:** NSAID-exacerbated cutaneous disease, **NIUAA:** NSAID-induced urticaria/angioedema/anaphylaxis, **np:** Not performed, **(+):** Positive, **RC:** Rhinoconjunctivitis, **SNIDR:** Selective NSAID-induced delayed-type hypersensitivity reaction, **SNIUAA:** Selective NSAID-induced urticaria/angioedema and/or anaphylaxis, **SPT: S**kin prick test, **SR:** Selective reactor, **U:** Urticaria

Table III: Risk Factors for NSAID-H

Univariate logistic regression analysis			95% CI	
Risk Factor	**p-value**	**OR**	**Min**	**Max**
Age over 10 years	0.006	3.818	1.459	9.989
Presence of allergic disease	0.048	2.727	1.009	7.370
Family history of drug allergy	0.033	3.588	1.105	11.648
Number of reactions greater than one	0.003	4.267	1.619	11.244
Presence of angioedema	0.016	5.000	1.343	18.620

could not be classified into a single group. A patient with asthma and allergic rhinitis developed angioedema and was classified as NIUAA. A detailed description of the clinical characteristics is presented in Table II.

Risk Factors of NSAID-H

Comparative analysis between the NSAID-H and tolerant groups was performed. No significant associations were found with gender, total IgE levels, eosinophil ratio, eosinophil count, basophil ratio, or basophil count ($p = 0.373$, $p = 0.289$, $p = 0.380$, $p = 0.887$, $p = 0.996$, and $p = 0.809$, respectively). No cases of NSAID-H were identified in patients under 2 years of age. The likelihood of NSAID-H is low in individuals under the age of two, while it is higher in those over the age of ten ($p = 0.009$). NSAID-H was found to be higher in individuals with a history of multiple reactions compared to the patients with a single reaction ($p = 0.002$). When compared based on the time interval between drug intake and the onset of the reaction (<1 hour, 1-24 hours, >24 hours), children with a reaction onset of less than one hour had a higher risk of NSAID-H ($p = 0.004$). The rate of NSAID-H was statistically significantly higher in patients with anaphylaxis and angioedema ($p = 0.004$). The likelihood of NSAID-H was significantly higher in patients with a history of allergic disease compared with those without such history ($p = 0.044$). The rate of having a family history of drug allergy was higher compared to those without such history ($p = 0.044$).

In univariate logistic regression analysis, being over 10 years old, having an allergic disease, a family history of drug allergy, having multiple reactions, and the presence of angioedema significantly increase the risk of NSAID-H (Table III).

In the multivariable logistic regression analysis, being older than 10 years was independently associated with NSAID-H (aOR 4.505; 95% CI 1.230-16.501; $p=0.023$). Similarly, angioedema as the clinical presentation was identified as an independent risk factor (aOR 4.756; 95% CI 1.028-22.001; $p=0.046$). Family history of drug allergy and the presence of allergic disease were not independently associated ($p=0.795$ and $p=0.274$, respectively).

DISCUSSION

The frequent occurrence of NSAID-H reactions in children, characterized by distinct phenotypes compared to those found in adults, underscores the importance of understanding these reactions. In our study, we evaluated clinical characteristics and risk factors and highlighted the diagnostic challenges of NSAID-H in children. Comparative analysis revealed that multiple reactions, reaction onset within 1 hour of drug intake, angioedema, presence of allergic disease, and a positive family history of drug allergy were more frequently observed in patients with NSAID-H compared to tolerant subjects. Moreover, multivariable analysis identified age above 10 years and angioedema as independent risk factors for NSAID-H. In contrast, gender, total IgE levels, eosinophil ratio, eosinophil count, basophil ratio, and basophil count showed no significant differences between hypersensitive and tolerant groups. Another important finding of our study was the frequent off-label use of NSAIDs in children. Therefore, our results suggest that ibuprofen, given its wide approval across pediatric age groups and potent COX-1 inhibition, may serve as a practical option for DPT in clinical practice. In addition, our study demonstrated that even in patients presenting with involvement of two organ systems or with a history of 2-4 reactions, DPT results were negative. This finding emphasizes the pivotal role of DPT in the accurate diagnosis of NSAID-H.

The frequency of suspected drug reactions varies across countries depending on differences in patterns of medication use (3,7). In our study, the most frequently suspected and diagnosed drug in cases of hypersensitivity was found to be ibuprofen, consistent with other study data from our country (7-9). Like our study, the positivity rates of DPTs with culprit drugs in studies by Topal et al. and Cousin et al. were reported to be 16.3% and 16.9%, respectively (8,10). However, in a multicenter study conducted by Mori et al. this rate was found to be 19.6% (3). When patients diagnosed based on their histories were included, 29% of those presenting with suspected reactions to NSAIDs received a diagnosis of NSAID-H in the study (11,12). In the

literature, the rate of NSAID-H in patients presenting with suspected drug reactions to NSAIDs ranges from 9.8% to 68% (11,12). In our study, 27% of the patients were diagnosed with NSAID-H.

Few studies have been conducted on the diagnostic value of skin tests in patients with selective hypersensitivity to paracetamol, and the existing studies have involved few cases (13-15). In a study by Paramo et al., two out of four patients with selective paracetamol hypersensitivity had positive skin test results with paracetamol (13). Conversely, in a study by Sipahi et al., none of the three patients indicated positive skin test results with paracetamol (16). Interestingly, in our study, in patients with selective paracetamol hypersensitivity, 75% (n=3) had skin tests (SPT and IDT) with paracetamol. Among patients, only one case showed a false-positive result. However, due to the limited number of confirmed cases with DPT, we did not calculate sensitivity and specificity values to avoid overinterpretation.

According to the literature, the most common reasons for referral in cases of suspected NSAID-H are skin symptoms such as urticaria and angioedema (3). In our study, there were no cases in which patients presented with isolated respiratory symptoms; however, 15% of the patients (n=14) described the presence of at least two systems (skin and mucosal findings, respiratory symptoms, and syncope). Among these patients 21% (n=3) had their diagnosis confirmed by DPTs, while 28% (n=4) were not considered to have NSAID-H following DPT. The outcomes of our study indicate the need to conduct DPTs when anaphylaxis is suspected.

In the literature, there are different results regarding risk factors for NSAID-H (3,8,17-19). In our study, presenting with angioedema and anaphylaxis was identified as a risk factor. Similar to the findings of Topal et al., in our study, the presence of angioedema and age over 10 years were identified as independent risk factors for NSAID-H (8). In the literature, age above 10 years has been associated with an increased risk of NSAID-H (3,10). Furthermore, there were no cases of NSAID-H in children under 2 years of age in our study. This situation can be explained by the fact that viral infections, which are common in young children, can mimic drug allergies, suggesting that the risk of NSAID-H may be lower in this age group.

Consistent with our findings, previous studies have reported that the risk of NSAID-H is significantly higher in patients who develop symptoms within the first 60 minutes after drug intake (7,12,20). They also noted an increased risk in those who reacted to two or more chemically unrelated NSAIDs based on history (18,20).

In the studies by Arıkoğlu et al. and Şimşek et al., a family history of NSAID-H was not identified as a risk factor (7,12). However, in the study by Yılmaz et al., similar to our findings, a family history of drug allergy was found to be significantly more frequent in the NSAID-H group (18). In contrast, while they did not identify the presence of allergic disease as a risk factor, our study demonstrated it to be a significant predictor (18).

Yılmaz et al. highlighted in their study that multiple reactions may be a poor predictor whereas Blanca et al. and Şimşek et al. reported that the number of reaction episodes is an important predictor (12,18,20). In some publications, patients with recurrent reactions are considered NSAID-H without undergoing DPT (9,17,21-24). In our study, even patients describing two to four reactions to NSAIDs had negative results in the provocation test. Although multiple reactions may appear to be a risk factor, these results underscore the necessity of DPT.

Yılmaz et al. also reported tolerability rates of 60% for paracetamol and 88.8% for nimesulide (18). In our study, paracetamol was tolerated in 95% of patients (n=19/20), while the tolerability rate for nimesulide was lower, at 63% (n=5/8). Additionally, two DPTs with meloxicam yielded negative results. However, in our study, a greater number of DPTs with alternative drugs were conducted compared to this study (18).

It is reported that the frequency of cross-reaction is more common in children (7,19). In our study, 4 patients were classified as CI, while 4 patients were classified as SR. However, since aspirin provocation testing was not performed in patients, the actual CI/SR proportion could not be fully evaluated. It is known that classification can be challenging in the presence of mixed reactions and accompanying allergic diseases in children (10,11). In our study, a patient (patient No. 5, Table II) diagnosed with CU, AR and asthma developed angioedema with ibuprofen and rhinoconjunctivitis with nimesulide during DPTs. According to the latest EAACI guidelines, when both systems are affected simultaneously, this could be evaluated as anaphylaxis and classified as NIUAA (4). However, we observed two different types of reactions developing at different times. According to the current classification, the

patient could not be classified into a single group due to both cutaneous and respiratory symptoms were present. We classified it as both NERD and NECD.

One patient with chronic urticaria and allergic rhinitis, who developed skin symptoms with ibuprofen and paracetamol, was classified as NECD (patient No. 2, Table II). Additionally, a patient (patient No. 18, Table II) who developed angioedema with three different NSAID drugs, and who also had concomitant asthma and rhinitis, was classified as NIUAA, highlighting that, as stated in the review by Cavkaytar, the clinical manifestation is not correlated with the underlying disease (11).

Our study has several strengths. First, pediatric patients with suspected NSAID-H were comprehensively evaluated using SPT, IDT, and DPTs, including a wide range of alternative drugs, which allowed for a detailed assessment of tolerance. Second, we analyzed potential risk factors for NSAID-H in children and compared them with existing literature. Importantly, we demonstrated that DPT remains essential for excluding the diagnosis, even in patients presenting with multiple reactions or involvement of two organ systems. Third, our findings highlighted that underlying allergic diseases do not always align with the current NSAID-H classification in the pediatric population. Finally, we emphasized the frequent off-label use of NSAIDs in children and showed that parental concerns about aspirin significantly limit its use in DPT, thereby creating diagnostic challenges specific to this age group.

However, the limitations of the study include the fact that DPT was not performed in some patients at high risk of NSAID-H, and DPT with aspirin was not conducted. In our country, aspirin is rarely prescribed due to concerns about Reye's syndrome. Families generally did not consent to the test due to the risks associated with DPT. We opted for a safer approach for children. As a result, some patients remained undiagnosed, and their condition was not classified. Additionally, since aspirin challenge was not performed, patients with multiple selective responses may have been misclassified as cross-reactors. In our study, only a small portion of patients who underwent DPT (20%) tested positive. Although our study supports the necessity of DPT, it highlights the challenging management and classification of NSAID-H in children.

Conflicts of Interest

The authors declare that there is no conflict of interest to disclose.

Funding

The authors declare that the study received no funding.

Acknowledgements

The authors declare that they did not use any source of support.

Author Contributions

Concept: **Deniz Ozceker,** Design: **Merve Karaca Sahin, Deniz Ozceker,** Data collection or processing: **Muhammed Fatih Erbay, Guler Yildirim, Hamit Bologur, Sefika Ilknur Kokcu Karadag,** Analysis or Interpretation: **Nilay Caliskan, Hilal Gungor,** Literature search: **Merve Karaca Sahin, Hilal Gungor,** Writing: **Merve Karaca Sahin, Nilay Caliskan,** Approval: **Merve Karaca Sahin, Muhammed Fatih Erbay, Nilay Caliskan, Guler Yildirim, Hamit Bologur, Hilal Gungor, Sefika Ilknur Kokcu Karadag, Deniz Ozceker.**

REFERENCES

1. Jares EJ, Sánchez-Borges M, Cardona-Villa R, Ensina LF, Arias-Cruz A, Gómez M, et al;Latin America Drug Allergy Interest Group. Multinational experience with hypersensitivity drug reactions in Latin America. Ann Allergy Asthma Immunol 2014;113(3):282-9.
2. Rubio M, Bousquet PJ, Gomes E, Romano A, Demoly P. Results of drug hypersensitivity evaluations in a large group of children and adults. Clin Exp Allergy 2012;42:123-30.
3. Mori F, Atanaskovic-Markovic M, Blanca-Lopez N, Gomes E, Gaeta F, Sarti L, et al. A Multicenter Retrospective Study on Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Children:A Report from the European Network on Drug Allergy (ENDA) Group. J Allergy Clin Immunol Pract 2020;8:1022-1031.e1.
4. Kidon M, Blanca-Lopez N, Gomes E, Terreehorst I, Tanno L, Ponvert C, et al. EAACI/ENDA Position Paper:Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. Pediatr Allergy Immunol 2018;29:-80.
5. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity:questionnaire. EAACI Interest group on drug hypersensitivity. Allergy 1999;54:999-1003.
6. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al; European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003;58(9):854-63.
7. Arikoglu T, Aslan G, Yildirim DD, Batmaz SB, Kuyucu S. Discrepancies in the diagnosis and classification of nonsteroidal anti-inflammatory drug hypersensitivity reactions in children. Allergol Int 2017;66:418-24.
8. Yilmaz Topal O, Kulhas Celik I, Turgay Yagmur I, Toyran M, Civelek E, Karaatmaca B, et al. Results of NSAID provocation tests and difficulties in the classification of children with nonsteroidal anti-inflammatory drug hypersensitivity. Ann Allergy Asthma Immunol 2020;125:202-7.

9. Guvenir H, Dibek Misirlioglu E, Vezir E, Toyran M, Ginis T, Civelek E, et al. Nonsteroidal anti-inflammatory drug hypersensitivity among children. Allergy Asthma Proc 2015;36:386-93.
10. Cousin M, Chiriac A, Molinari N, Demoly P, Caimmi D. Phenotypical characterization of children with hypersensitivity reactions to NSAIDs. Pediatr Allergy Immunol 2016;27:743-8.
11. Cavkaytar O, du Toit G, Caimmi D. Characteristics of NSAID-induced hypersensitivity reactions in childhood. Pediatr Allergy Immunol 2019;30:25-35.
12. Eser Simsek I, Cogurlu MT, Aydogan M. Two approaches for diagnosis of nonsteroidal anti-inflammatory drug hypersensitivity in children. Ann Allergy Asthma Immunol 2019;123:389-93.
13. Paramo BJ, Gancedo SQ, Cuevas M, Camo IP, Martin JA, Cosmes EL. Paracetamol (acetaminophen) hypersensitivity. Ann Allergy Asthma Immunol 2000;85:508-11.
14. Numata T, Fukushi R, Ito T, Tsuboi R, Harada K. Acetaminophen anaphylaxis diagnosed by skin prick test. Allergol Int 2016;65:490-1.
15. Tsujino Y, Okamoto N, Morita E. Acetaminophen-induced urticaria without aspirin intolerance. J Dermatol 2007;34:224-6.
16. Sipahi Cimen S, Yucel E, Ozceker D, Suleyman A, Hizli Demirkale Z, Sayili U, et al. Behind the scene:Paracetamol hypersensitivity in children. Pediatr Allergy Immunol 2020;32:177-85.
17. Hassani A, Ponvert C, Karila C, Le Bourgeois M, De Blic J, Scheinmann P. Hypersensitivity to cyclooxygenase inhibitory drugs in children:a study of 164 cases. Eur J Dermatol 2008;18:561-5.
18. Yilmaz O, Ertoy Karagol IH, Bakirtas A, Topal E, Celik GE, Demirsoy MS, et al. Challenge-proven nonsteroidal anti-inflammatory drug hypersensitivity in children. Allergy 2013;68:1555-61.
19. Blanca-López N, Haroun-Diaz E, Ruano FJ, Pérez-Alzate D, Somoza ML, Vázquez de la Torre Gaspar M, et al. Acetyl Salicylic Acid Challenge in Children with Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs Differentiates Between Cross-Intolerant and Selective Responders. J Allergy Clin Immunol Pract 2018;6(4):1226-35.
20. Blanca-Lopez N, J Torres M, Doña I, Campo P, Rondón C, Seoane Reula ME, et al. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. Clin Exp Allergy 2013;43(1):85-91.
21. Blanca-López N, Pérez-Sánchez N, Agúndez JA, García-Martin E, Torres MJ, Cornejo-García JA, et al. Allergic Reactions to Metamizole: Immediate and Delayed Responses. Int Arch Allergy Immunol 2016;169(4):223-30.
22. Kidon MI, Liew WK, Chiang WC, Lim SH, Goh A, Tang JP, et al. Hypersensitivity to Paracetamol in Asian Children with Early Onset of Nonsteroidal Anti-Inflammatory Drug Allergy. Int Arch Allergy Immunol 2007;144:51-6.
23. Kidon MI, Kang LW, Chin CW, Hoon LS, See Y, Goh A, et al. Early Presentation With Angioedema and Urticaria in Cross-reactive Hypersensitivity to Nonsteroidal Antiinflammatory Drugs Among Young, Asian, Atopic Children. Pediatrics 2005;116:e675-80.
24. Doña I, Pérez-Sánchez N, Bogas G, Moreno E, Salas M, Torres MJ. Medical algorithm:Diagnosis and treatment of nonsteroidal antiinflammatory drugs hypersensitivity. Allergy 2020;75:1003-5.