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Original Article

Discrepancies in the diagnosis and classification of nonsteroidal anti-inflammatory drug hypersensitivity reactions in children

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NSAID, Nonsteroidal anti-inflammatory drugs; CIs, cross-intolerants; SRs, selective responders; ENDA, European Network for drug Allergy; DPT, drug provocation test; NERD, NSAID-exacerbated respiratory disease; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; SNIUAA, single NSAID-induced urticaria/angioedema and/or anaphylaxis; SNIDR, single NSAID-induced delayed reactions; SPTs, skin prick tests; IDTs, intradermal tests; FEV1, forced expiratory volume in 1 s; aOR, adjusted odds ratio

ABSTRACT

Background: Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently encountered in daily clinical practice. The aim of this study was to determine the confirmation rates, risk factors of NSAID hypersensitivity in children and to try to classify them with a standardized diagnostic protocol.
Methods: All patients with a suspicion of NSAID-induced hypersensitivity were evaluated with European Network for drug Allergy (ENDA) recommendations. The children were classified as selective responders (SRs) or cross-intolerant (CI) depending on the drug provocation test (DPT) results.
Results: We evaluated 106 children with a suspicion of NSAID hypersensitivity. NSAID hypersensitivity was confirmed with tests in 31 patients; 4 (12.9%) were diagnosed by skin tests and 27 (87.1%) by DPTs and two patients with a history of anaphylaxis by medical records. Eleven patients (33.3%) were classified as SRs, whereas twenty-two (66.6%) children as CIs. SRs and CIs were further classified as NSAID-induced urticaria/angioedema (n = 8), NSAID-exacerbated cutaneous disease (n = 6) and NSAID-exacerbated respiratory disease (n = 1) and single NSAID-induced urticaria/angioedema and/or anaphylaxis (n = 11). Eight (24.2%) patients could not be categorized according to ENDA/GA^{2}LEN classification; one CI patient could not be classified based on pathomechanisms, seven CIs could not be categorized based on the underlying disease and clinical manifestations. A reaction within an hour of drug intake (aOR:3.0, 95% confidence interval: 1.18–7.67, $p = 0.021$), a history with multiple NSAIDs hypersensitivity (aOR:2.9, 95% confidence interval: 1.16–7.60, $p = 0.022$), and family history of atopy (aOR:4.0, 95% confidence interval: 1.50–10.82, $p = 0.006$) were found as the independent risk factors related to confirmed NSAID hypersensitivity.
Conclusions: This study suggests the presence of different phenotypes which do not fit into the current classifications in children with NSAID hypersensitivity.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly prescribed group of drugs in children. Hypersensitivity to NSAIDs are of great concern because they are frequently encountered in daily clinical practice.[1] Although the overall prevalence of NSAID hypersensitivity has been reported between 0.6 and 5.7% of the general population, the results vary significantly depending on the population studied and the method of assessment.[2,3] In children, the reported prevalence of NSAID hypersensitivity is 0.3%, and the aspirin sensitivity in children with asthma is 5%, as assessed by provocation tests.[4,5] Proposed risk factors for NSAID-induced hypersensitivity reactions are older age, the number of drugs taken, chronic urticaria, a previous history of anaphylaxis, immediate reactions, and the family history of NSAID hypersensitivity.[6–8] Among other conditions, atopy was reported as a risk factor for NSAID hypersensitivity.[9,10]

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The diagnosis of hypersensitivity reactions to NSAIDs is usually based on patient history. However it is mostly misleading, and a standardized diagnostic work-up is necessary for a definitive diagnosis.[11,12] A complete allergy work-up should include a detailed clinical history of the patient's reaction, associated risk factors and reaction interval. NSAID associated reactions are divided into two major categories according to the underlying mechanisms: reactions without previous immunological recognition (cross-hypersensitive type reactions) or through immunological mechanisms (allergic or selective reactions) involving specific IgE antibodies (immediate reactions) or T cells (delayed reactions).[13,14] Patients with immediate reactions (reactions <24 h after drug intake) to NSAIDs may be selective responders (SRs, hypersensitive to only one type of NSAID) or cross-intolerants (CIs, hypersensitive to more than one chemically unrelated NSAID).[15,16] Recently, European Network for drug Allergy (ENDA) has further classified CIs into three subgroups and SRs into two subgroups.[13] Kowalski *et al.*, classified NSAID hypersensitivity as NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria/angioedema (NIUA) and single NSAID-induced urticaria/angioedema and/or anaphylaxis (SNIUAA) and single NSAID-induced delayed reactions (SNIDR) in 2013.[13] Clinical observations and the data in the literature showed that some patients with confirmed NSAID hypersensitivity could not be categorized according to ENDA classification.[17] The proper evaluation and classification of children with NSAID hypersensitivity according to different phenotypes is essential due to the fact that it is a really important and complex issue in pediatric population.

Despite recent developments in the area of drug allergy, current classification system may not be sufficient to categorize all the children with a diagnosis of NSAID hypersensitivity. The purposes of this study were to determine the confirmation rates of clinician or parent reported NSAID hypersensitivity reactions in Turkish children and to try to classify them with a standardized diagnostic protocol based on ENDA guideline[13] and also to search for risk factors related to confirmed NSAID hypersensitivity. As a secondary aim, an investigation was conducted to determine safe alternative drugs for children with actual NSAID hypersensitivity.

Methods

Study population

The children referred to the Pediatric Allergy Clinic of Mersin University with a suspicion of NSAID-induced hypersensitivity reaction were evaluated between January 2009 to April 2016. Patients with a history of acute reactions (reaction time; immediate to several hours) such as urticaria/angioedema, bronchospasm, laryngeal edema and systemic reactions were included in the study. Delayed reactions (reaction time; more than 24 h after exposure) were not included. The Mersin University Hospital ethics committee approved this study. Prior to this study, parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained.

Data collection

A comprehensive ENDA questionnaire was applied to the children with a history of NSAID allergy suspicion by the clinician or patient perspective.[18] This questionnaire comprised questions about demographic data, culprit drugs, reaction interval, characteristics of index drug reaction, management procedures and family and personal histories of drug allergy and atopy. The questionnaire was performed by a clinician using information provided by the parents or referring physician.

Atopy was assessed by questionnaire, food and inhalant specific IgE levels, serum total IgE, peripheral eosinophil counts and skin prick tests (SPTs) with inhalant allergens. The following inhalant antigens were applied to the volar surface of the forearm in addition to histamine and saline controls: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach, cat and dog dander, Alternaria, mixed grass and tree pollen. A test was considered positive if the mean diameter of the wheal was $\geq$3 mm compared with the negative control.

Diagnostic evaluation

According to ENDA recommendations, the patients who had a history of immediate reactions to a single NSAID were classified as SR and tested by skin prick and intradermal tests (İDTs) and, if negative tests, were challenged with the culprit drug. In case of positive challenge, additional drug provocation tests (DPTs) were performed with ibuprofen or acetylsalicylic acid to confirm or exclude cross-reactivity. The patients with a history of hypersensitivity reactions to more than one chemically unrelated NSAIDs were classified as CI group and directly challenged with culprit drugs based on ENDA recommendations. In those cases with a positive DPT to the culprit drug, another challenge with potent COX1 inhibitors, such as ibuprofen or acetylsalicylic acid was performed.[13] SRs and CIs were further categorized according to the ENDA/GA^{2}LEN classification; NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria/angioedema (NIUA) and single NSAID-induced urticaria/angioedema and/or anaphylaxis (SNIUAA).[13]

Skin tests

Antihistamine medications and drugs that could affect skin tests were stopped 1 week before testing. SPTs with undiluted injectable forms and IDTs with 1/10 dilutions (0.1 mg/ml concentration) were used according to maximum non-irritant concentrations as recommended by ENDA.[19] Skin prick tests with acetaminophen (Perfalgan, 10 mg/ml), metamizole sodium (Novalgin, 1 g/2 ml) and diclofenac (Voltaren 75 mg/3 ml) were performed at concentrations of 10 mg/ml, 0.4 mg/ml and 25 mg/ml, respectively. A SPT was considered as positive if the wheal was at least 3 mm larger than the negative control with surrounding erythema. If SPTs were negative, 0.02 ml of the relevant agent was injected intradermally on volar forearm skin, and the reaction was evaluated 20 min later. When the mean diameter of the bleb created by the injection increased by 3 mm or more with surrounding erythema, then the results were considered as positive. In SPTs and IDTs, histamine at 10 and 1 mg/ml were used for positive controls respectively, and normal saline was used as a negative control.[19,20]

Drug provocation tests

In all children, except those with severe reactions, or if performed, skin test positive patients, oral DPTs were performed. An initial dose of 1/10,000–1/100 of the therapeutic dose was administered depending on the severity of the reaction. Four or five escalating doses of the culprit drug were administered during DPT with the intervals of 30–60 min up to a cumulative dose of maximum daily dose. The challenge doses were based on the recommendations of ENDA and were modified according to the weight of the children.[21,22] The children were kept under strict medical observation for up to 2 h after completing the test. If no sign of drug hypersensitivity reaction occured, then challenges were continued for 2 days to diagnose delayed responses. The DPT test was considered positive if any objective symptoms or signs such as

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urticaria, angioedema, rhinorrhoea, sneezing, bronchospasm, dyspnea, hypotension, anaphylaxis or a >15% decrease in forced expiratory volume in 1 s (FEV1) were observed during the test.[23] In case of a positive reaction, the tests were stopped and the patients were treated symptomatically.

Drug provocation tests for safe alternative drugs

To find safe alternatives in children with confirmed NSAID hypersensitivity, DPTs were conducted. In children <12 years old, DPTs were carried out with acetaminophen. In children ≥12 years old, nimesulide or meloxicam were tested to find a safe alternative. In a case of a positive reaction, the tests were stopped and the patients were treated.

Statistical analysis

Statistical analyses were performed using the SPSS 11.5.1 statistical software for Windows. Mann–Whitney test was used for the comparison of continuous variables and chi-square test was used for the comparison of categorical variables. A logistic regression analysis was used to investigate the associations between NSAID hypersensitivity and clinical characteristics. The possible risk factors for confirmed NSAID allergy identified with univariate analysis ($p < 0.1$) were included in the multiple logistic regression analysis. The adjusted odds ratio (aOR) and its 95% confidence interval were calculated. A p value of <0.05 was considered to be significant.

Results

Study population

We evaluated 106 children referred to the Pediatric Allergy Clinic of Mersin University with a suspicion of NSAID-induced hypersensitivity. The median age of the subjects was 6 years old (min: 1 year max: 18 years) and 48 (45.3%) were female. Fifty-seven patients (53.8%) described a reaction to a single NSAID, whereas 49 (46.2%) children against multiple NSAIDs. Ibuprofen (63.8%) and acetaminophen (59%) were the most frequently reported culprit drugs in the reaction history. Thirty-nine patients (36.8%) reported NSAID reactions within the first hour. Urticaria was the most common reaction affecting a total of 59 patients (55.7%) followed by urticaria with angioedema (26.4%), only angioedema (12.3%), anaphylaxis (4.7%) and respiratory involvement (0.9%). Among all subjects, 14 (13.2%) had family histories of NSAID allergy, and 45 (42.5%) had physician-diagnosed allergic disorders (asthma, allergic rhinitis, food allergy, and chronic urticaria).

Results of diagnostic tests

Of the 106 patients with a history of NSAID hypersensitivity evaluated, 31 were confirmed with tests. Of the 31 patients with confirmed reactions, 4 (12.9%) were diagnosed by skin tests and 27 (87.1%) by DPT. NSAID hypersensitivity in two patients with a history of doctor diagnosed anaphylaxis was confirmed by medical records and DPTs were not performed in such high risk patients based on ENDA recommendations (Fig. 1) (Table 1).

Patients with a reaction history to a single NSAID

Among 57 subjects with a reaction history to a single NSAID, 54 had urticaria and/or angioedema and 3 had anaphylaxis. Ibuprofen (45.6%) was the most frequently reported culprit drug followed by acetaminophen (36.8%) and metamizole (10.5%) in this group. Skin tests could be performed on 35 patients. Of these, 4 had positive IDT results (three patients with metamizole and one patient with acetaminophen). The skin tests of the remaining 31 patients were negative. In 21 patients, skin tests were not available (the parents of 17 patients did not give consent for skin tests, 1 patient had egzema on the test area and 3 patients had dermatographism). Fifty-two patients were challenged with the culprit drug. One patient was not challenged because of the doctor diagnosed history of anaphylaxis. Including this patient with anaphylaxis, single NSAID-

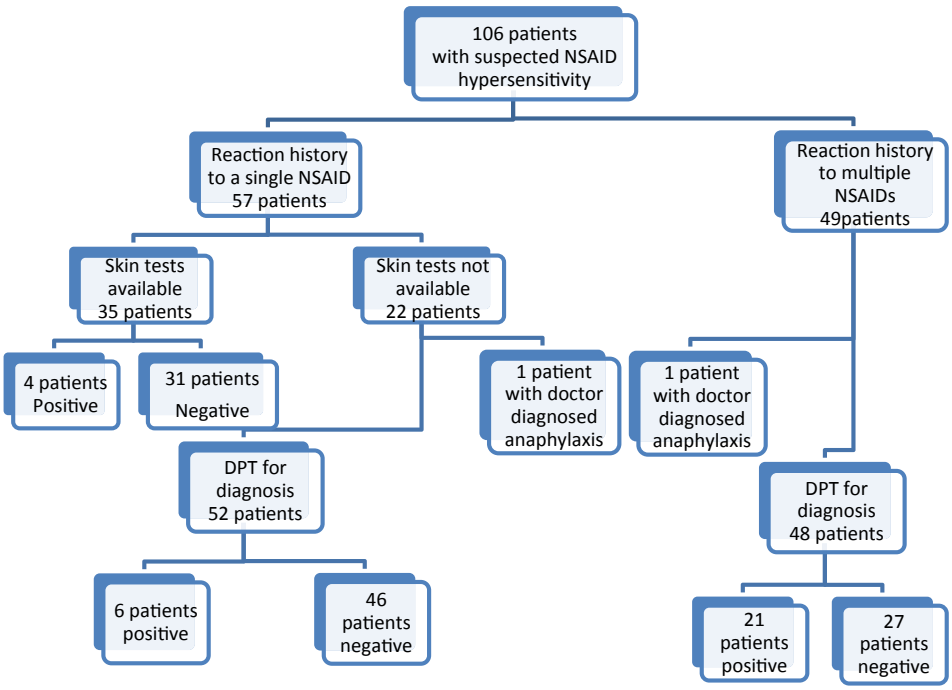

Fig. 1. Diagnostic flow chart for 106 patients with suspected NSAID hypersensitivity.

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Table 1
The patients with confirmed NSAID hypersensitivity.

Patient	Age, years	SR/CI	Allergic disease	Culprit drug	Skin test result	Drug Provocation	Reaction during DPT	Classification according to ENDA	Safe alternative
1	17	CI	–	Ibuprofen Flurbiprofen Metamizole	NA	Ibuprofen Metamizole	AO AO	NIUA	Acetaminophen
2	6	CI	–	Ibuprofen Metamizole	NA	Ibuprofen Metamizole	AO AO	NIUA	Acetaminophen
3	5	CI	–	Acetaminophen Ibuprofen	NA	İbuprofen ASA	AO AO	NIUA	Acetaminophen
4	15	CI	Asthma	Acetaminophen Ibuprofen	NA	Acetaminophen Ibuprofen	AO AO	Unclassified	Meloxicam
5	9	CI	Asthma	Ibuprofen Metamizole	NA	Ibuprofen Metamizole	AO AO	Unclassified	Acetaminophen
6	7	CI	CU	Acetaminophen Ibuprofen	NA	Ibuprofen ASA	U U	NECD	Acetaminophen (low dose)
7	14	SR	–	Metamizole	IDT (+)	NP Ibuprofen	NP (−)	SNIUA	Acetaminophen
8	14	SR	AR	ASA	Negative	ASA Ibuprofen	AO (−)	SNIUA	Acetaminophen Metamizole†
9	5	CI	–	Acetaminophen Ibuprofen	NA	Ibuprofen ASA	AO AO	NIUA	Acetaminophen
10	10	CI	Asthma	Acetaminophen Ibuprofen	NA	Ibuprofen ASA	U U	Unclassified	Acetaminophen
11	6	SR	–	Metamizole	IDT (+)	NP Ibuprofen	NP (−)	SNIUA	Acetaminophen
12	11	CI	–	Acetaminophen Ibuprofen Metamizole	NA	Ibuprofen Metamizole	AO AO	NIUA	Acetaminophen
13	6	SR	AR	Ibuprofen	Negative	Ibuprofen ASA	U, AO (−)	SNIUA	Acetaminophen
14	12	CI	CU	Acetaminophen Ibuprofen	NA	Acetaminophen Ibuprofen	U, AO U, AO	NECD	Nimesulide
15	6	SR	–	Acetaminophen	Negative	Acetaminophen Ibuprofen	U (−)	SNIUA	Acetaminophen (low dose)
16	18	SR	–	Metamizole	Negative	Metamizole Ibuprofen	A (−)	SNIUA	Acetaminophen
17	3	CI	Asthma	Ibuprofen Metamizole	NA	Ibuprofen Metamizole	U, AO U, AO	Unclassified	Acetaminophen (low dose)
18	12	SR	Asthma	Acetaminophen	Negative	Acetaminophen Ibuprofen	U (−)	SNIUA	Ibuprofen
19	6	CI	CU	Acetaminophen Ibuprofen	NA	İbuprofen ASA	U U	NECD	Acetaminophen
20	5	SR	–	Ibuprofen	Negative	İbuprofen ASA	U (−)	SNIUA	Acetaminophen
21	15	CI	CU	Acetaminophen Naproxen ASA	NA	ASA Naproxen Acetaminophen	U U U	NECD	Metamizole†
22	5	CI	–	Acetaminophen Ibuprofen	NA	İbuprofen ASA	U U	NIUA	Acetaminophen
23	16	CI	CU	Acetaminophen Ibuprofen	NA	İbuprofen ASA	U, AO U, AO	NECD	Acetaminophen
24	6	CI	AR Asthma	Acetaminophen Ibuprofen Metamizole	NA	Acetaminophen İbuprofen Metamizole	U U U	Unclassified	Acetaminophen (low dose)†
25	10	CI	CU	İbuprofen ASA	NA	İbuprofen ASA	U A	Unclassified	Acetaminophen
26	3	CI	CU	İbuprofen Metamizole	NA	İbuprofen Metamizole	AO AO	NECD	Acetaminophen
27	6	CI	–	Acetaminophen Ibuprofen	NA	İbuprofen ASA	U U	NIUA	Acetaminophen
28	17	CI	–	Acetaminophen Diclofenac	NA	Ibuprofen Diclofenac	U U	NIUA	Meloxicam
29	2	SR	–	Metamizole	IDT (+)	NP Ibuprofen	NP (−)	SNIUA	Acetaminophen
30‡	8	SR	–	Metamizole	NA	NP Ibuprofen	NP (−)	SNIUA	Acetaminophen
31‡	17	CI	CU	Acetaminophen Ibuprofen	NA	NP NP	NP NP	Unclassified	Meloxicam
32	2	SR	–	Acetaminophen	IDT (+)	NP Ibuprofen	NP (−)	SNIUA	İbuprofen
33	15	CI	Asthma	ASA Ibuprofen	NA	ASA Ibuprofen	>15% ↓ in EV1	NERD	Acetaminophen

A, Anaphylaxis; AO, Angioedema; ASA, Acetylsalicylic acid; AR, Allergic rhinitis; CU, Chronic urticaria; IDT, Intradermal test; NA, Not applicable; NP, Not provocated; Np, Not performed; U, Urticaria; SR, Selective responder; CI, Cross-intolerant.

† Patients had already been using these safe alternative drugs.

‡ The patients with doctor diagnosed anaphylaxis.

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induced hypersensitivity was confirmed in 11 of 57 patients (19.3%).

Patients with a reaction history to multiple NSAIDs

Among 49 subjects with a reaction history to multiple NSAIDs, 46 patients had urticaria and/or angioedema, 2 had anaphylaxis and 1 had respiratory involvement. Acetaminophen with ibuprofen (58.3%) were the most frequently reported culprit drug combination in this group. Forty-eight patients were challenged with the culprit drug. One patient was not challenged because of the doctor diagnosed history of anaphylaxis. Including this patient with anaphylaxis confirmed with medical records, multiple NSAIDs-induced hypersensitivity was confirmed in 22 of 49 patients (44.9%).

Classification of patients with confirmed NSAID hypersensitivity according to ENDA

SRs and CIs were further classified as NSAID-induced urticaria/angioedema (n = 8), NSAID-exacerbated cutaneous disease (n = 6) and NSAID-exacerbated respiratory disease (n = 1) and single NSAID-induced urticaria/angioedema and/or anaphylaxis (n = 11). Seven CIs could not be categorized according to ENDA classification system based on the patients' clinical manifestations and the underlying diseases (Table 1).

Drug provocation tests and safe alternatives

The patients with confirmed NSAID hypersensitivity were challenged to find safe alternative drugs. Acetaminophen was found to be a safe alternative in 26 patients including four with low dose. 3 patients tolerated meloxicam, 1 patient tolerated nimesulide. Ibuprofen was found as a safe alternative in 2 patients. Two patients had already been using metamizole as safe alternative drug and their parents did not consent DPT for metamizole (Table 1).

We found a patient (Patient no: 8 in Table 1) showing a selective reaction to acetylsalicylic acid. He had already been using acetaminophen and metamizole as safe alternatives. Another patient (Patient no: 21 in Table 1) reacted to acetylsalicylic acid, naproxen and also acetaminophen but tolerated metamizole. This patient with no underlying disease could not be categorized by current classifications based on pathomechanisms and COX-1 inhibition. The other patient encountered anaphylaxis with acetylsalicylic acid and urticaria with ibuprofen (Patient no: 25 in Table 1).

We found 9 (27.2%) patients with acetaminophen hypersensitivity. Three of these patients were SRs and six of them were CIs. Four of these nine patients with confirmed acetaminophen hypersensitivity tolerated acetaminophen at low doses but reacted at maximum daily doses (Patient no: 6, 15, 17 and 24 in Table 1).

Risk factors related to confirmed NSAID hypersensitivity

When we compared the possible risk factors of the groups with (n = 33) and without (n = 73) confirmed NSAID hypersensitivity, we found that a reaction developing within an hour of drug intake ($p = 0.007$), a history of having a reaction with multiple NSAIDs ($p = 0.007$), and family history of atopy ($p = 0.002$) were significantly higher in the confirmed NSAID hypersensitivity group. There was no significant difference between the groups with and without confirmed NSAID hypersensitivity in terms of age, gender, personal atopy, serum total IgE, peripheral eosinophilia and the presence of NSAID hypersensitivity in the family (Table 2).

Table 2
The comparison of patients in the groups with confirmed NSAID hypersensitivity and without NSAID hypersensitivity.

Variable	Patients with not confirmed NSAID hypersensitivity n = 73 (%)	Patients with confirmed NSAID hypersensitivity n = 33 (%)	*P* value
Female gender	36 (49.3)	12 (36.4)	0.263
Age[†] (years)	5 (1–18)	8 (2–18)	0.063
Atopic sensitization	21 (28.7)	9 (27.3)	0.947
Atopic disease	27 (36.9)	18 (54.5)	0.178
Asthma	11 (15)	7 (21.2)	0.628
Allergic rhinitis	5 (6.8)	3 (9.1)	0.964
Chronic urticaria	10 (13.6)	8 (24.2)	0.251
Food allergy	1 (1.3)	0	0.637
Family history of atopy	13 (17.8)	16 (48.5)	**0.002**
Family history of NSAID allergy	9 (12.3)	5 (15.1)	0.909
Clinical presentations			
Urticaria	49 (67.1)	10 (30.3)	**0.001**
Angioedema	9 (12.3)	4 (12.1)	0.769
Urticaria and angioedema	15 (20.5)	13 (39.4)	0.057
Anaphylaxis	0	5 (15.1)	**0.003**
Respiratory involvement	0	1 (3.0)	0.678
Reaction with multiple NSAIDs	27 (36.9)	22 (66.6)	**0.007**
Reaction with a single NSAID	46 (63)	11 (33.3)	
	21 (28.7)	18 (54.5)	
Reaction within first hour after drug intake			**0.007**
Serum total IgE[†] (IU/mL)	90.5 (4–1080)	89 (17–986)	0.268
Serum eosinophilia[†]	140 (10–670)	150 (10–1110)	0.230

p values in bold are significant.
[†] Data are presented as median (min–max).

Multiple logistic regression analysis revealed that the presence of multiple NSAIDs hypersensitivity (aOR: 2.9, 95% confidence interval: 1.16–7.60, $p = 0.022$) and a reaction within an hour of drug intake (aOR: 3.0, 95% confidence interval: 1.18–7.67, $p = 0.021$) were found as the independent risk factors related to confirmed NSAID hypersensitivity. In addition, the patients with family history of atopy were 4 times more likely to have a confirmed NSAID hypersensitivity than those without (aOR: 4.0, 95% confidence interval: 1.50–10.82, $p = 0.006$) (Table 3).

When we evaluated the risk factors related to confirmed NSAID hypersensitivity in each group (CI and SR) in multiple logistic regression analysis, a reaction within an hour of drug intake (aOR: 5.9, 95% confidence interval: 1.11–32.33, $p = 0.037$) was found as the only risk factor in SRs whereas a history of family atopy (aOR: 6.8, 95% confidence interval: 1.27–37.16, $p = 0.025$) was found as the only risk factor in CIs.

Table 3
Multiple logistic regression analysis of factors related to confirmed NSAID hypersensitivity.

Variable	Odds ratio (95% confidence interval)	*P* value
Age	1.06 (0.96–1.18)	0.215
Female gender	2.11 (0.78–5.73)	0.140
Presence of atopic disease	0.86 (0.29–2.55)	0.798
Family history of atopy	4.04 (1.50–10.82)	**0.006**
Family history of NSAID hypersensitivity	1.20 (0.35–4.11)	0.765
Reactions with multiple NSAIDs	2.97 (1.16–7.60)	**0.022**
Reaction within the first hour of drug intake	3.01 (1.18–7.67)	**0.021**
Serum eosinophilia	1.00 (0.99–1.00)	0.823

p values in bold are significant.

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Discussion

The present study aimed to reveal the confirmation rate of NSAID hypersensitivity reactions and related risk factors in children and to try to classify them with current classification system. We evaluated 106 children, and 33 (31.1%) of the patients with suspected reactions were confirmed as NSAID hypersensitivity (including two patients with anaphylaxis confirmed with medical records). A reaction within an hour of drug intake, the presence of multiple NSAIDs hypersensitivity and family history of atopy were found as the independent risk factors related to confirmed NSAID hypersensitivity. Acetaminophen was shown to be well tolerated in patients <12 years with NSAID hypersensitivity whereas nimesulide and meloxicam are well tolerated in children ≥12 years. Furthermore, our study suggested the presence of different phenotypes which do not fit into the current classifications in children with NSAID hypersensitivity.

One of the most frequently implicated groups of drugs responsible for hypersensitivity reactions are NSAIDs since they are among the mostly prescribed drugs worldwide.[24] A previous study evaluated 63 children with histories of NSAID hypersensitivity, confirming 68.2% as allergic.[10] NSAID hypersensitivity was reported to be 52.3% in Latin America. Of the 862 patients evaluated, 20.6% were children and teenagers.[25] In Norway and Turkey, NSAID hypersensitivity was reported to be 32% and 21.1%, respectively.[26,27] In the present study, 31.1% of the suspected NSAID reactions were confirmed, similar to a study by Demir, which obtained a confirmation rate of 25%.[28]

It has been reported that reactions with single NSAID represent around 20% of NSAID hypersensitivity in Denmark[29] whereas this rate increases to 41.9% in Spain.[10] In the work by Dona *et al.*, which includes the largest series of subjects suffering from hypersensitivity reactions to NSAIDs, the most frequently confirmed diagnosis was hypersensitivity to multiple NSAIDs (76%).[30] Yilmaz *et al.*, investigated NSAID hypersensitivity in 58 children, confirming single-drug-induced and cross-reactive NSAID allergy in 5 of 36 (14%) and 8 of 18 (44%), respectively.[8] In the present study, NSAID hypersensitivity was diagnosed in 33 (31.1%) of the 106 patients, 66.6% of which were the cross-reactive type.

Ibuprofen was the most frequently implicated NSAID in our study, followed by acetaminophen. This is consistent with previous results.[10,31] The most important drugs involved in cross-reactive type group were ibuprofen, and acetaminophen and in SR group ibuprofen, followed by acetaminophen and metamizole in our study. In Dona's study, the most implicated drugs involved in cross-intolerance were propionic acid derivatives, in most cases ibuprofen, and in selective responders pyrazolones.[30] Another study found the leading cause of NSAID hypersensitivity was metamizole followed by aspirin among the 308 adult patients.[28]

NSAID hypersensitivity was confirmed with tests in 31 patients; 4 (12.9%) were diagnosed by skin tests and 27 (87.1%) by DPTs. NSAID hypersensitivity was confirmed in two patients with a history of anaphylaxis by medical records. Eventually, the diagnosis of NSAID hypersensitivity was largely based on DPTs. In patients with multiple NSAID hypersensitivity, DPTs are also of great importance in establishing or excluding drug allergy and for suggesting safe analgesic drugs.

We have found a patient showing selective reaction to acetylsalicylic acid (Patient no: 8 in Table 1) in our study. The existence of such patients has been reported previously.[10,28] Moreover, one of our CI patients (Patient no: 21 in Table 1) reacted to acetylsalicylic acid, naproxen and also acetaminophen but tolerated metamizole. This patient with no underlying disease could not be categorized by current classifications based on pathomechanisms and COX-1 inhibition. However, it may be related to the chemical structures of the NSAIDs. Therefore, multiple NSAID hypersensitivity should be evaluated in a broader sense, including chemical structure and other factors in addition to COX-1 inhibition.

In our study, SRs and CIs were further classified as NSAID-induced urticaria/angioedema (n = 8), NSAID-exacerbated cutaneous disease (n = 6) and NSAID-exacerbated respiratory disease (n = 1) and single NSAID-induced urticaria/angioedema and/or anaphylaxis (n = 11). Seven CIs could not be categorized according to ENDA/GA^{2}LEN classification system. Five asthmatic patients who developed urticaria to several NSAIDs could not be categorized based on underlying disease (Patient no: 4, 5, 10, 17 and 24 in Table 1). According to ENDA classification, asthma was defined as an underlying disease in only NERD (NSAIDs-exacerbated respiratory disease) in CI subjects. Also, two patients with chronic urticaria could not be classified; one patient with chronic urticaria encountered anaphylaxis with acetylsalicylic acid and urticaria with ibuprofen (Patient no: 25 in Table 1) and the other patient with chronic urticaria encountered anaphylaxis with acetaminophen and ibuprofen (Patient no: 31 in Table 1). Although anaphylaxis was reported in CI subjects in previous studies, this phenotype does not exist in ENDA classification.[28,30] In ENDA classification, only NECD was defined for cross-intolerant patients with chronic urticaria as an underlying disease. Cousin *et al.*, found that 43 patients (40.2%) could not be classified following the ENDA recommendations. They reported that the main discrepancies were on the patients' clinical manifestations and their possible underlying diseases.[32] Cavkaytar *et al.*, showed that five patients (4.5%) could not be categorized according to current classification systems.[33]

Acetaminophen hypersensitivity in patients with cross-reactive type NSAID hypersensitivity was reported to be up to 25% of pediatric patients[6,10,34] and 34% in adults.[35] We found 9 (27.2%) patients with confirmed acetaminophen hypersensitivity. Three of these patients were SRs and six of them were CIs. Also, four of the patients with confirmed acetaminophen hypersensitivity tolerated acetaminophen at low doses but reacted at higher doses.

Children with confirmed NSAID hypersensitivity were challenged to find safe alternative drugs in our study. Acetaminophen was shown to be well tolerated in patients <12 years with NSAID hypersensitivity whereas nimesulide and meloxicam were well tolerated in children ≥12 years. Yilmaz *et al.*, used tolmetin sodium for the children <12 years with acetaminophen hypersensitivity and nimesulide and meloxicam for the children ≥12 years with NSAID hypersensitivity as safe alternatives.[8]

Potential risk factors for NSAID hypersensitivity have been defined in various reports.[33,36] Risk factors include female sex, older age, the number of drugs taken, a previous history of anaphylaxis and immediate reactions.[6,7,10] Recent studies reported a significant association between NSAID hypersensitivity and atopy.[9,30] Yilmaz *et al.*, determined that family history of NSAID hypersensitivity was the only significant predictor of DPTs.[8] In our study, a reaction within an hour of drug intake, the presence of multiple NSAIDs hypersensitivity and family history of atopy were found as the independent risk factors for NSAID hypersensitivity. The association between the presence of a reaction history with more than one NSAID and confirmed hypersensitivity may due to the fact that the most of the children with confirmed drug allergy in our study are cross-intolerant. Nevertheless, a reaction history with more than one NSAID may be more reliable than a reaction history with one NSAID for predicting real drug hypersensitivity. On the other hand, the reason for the association between atopy and confirmed NSAID hypersensitivity is not known, although it has been suggested that genetic factors may be involved. In fact, genes implicated in the IgE response (IL-4, IL-5 and IL-13) are located in the same chromosomal region as the cysteinyl leukotriene (LTC4S).[37,38]

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The limitation of our study was the relatively small number of subjects analyzed and it was a restrospective investigation based on chart reviews. However, our study had several strengths. First, the patients were evaluated by a detailed questionnaire and a diagnostic protocol. Second, there is still limited data about NSAID hypersensitivity in children, so that the data in this study have provided important additive results about divergent phenotypes of NSAID hypersensitivity in Turkish children besides the frequency and risk factors of NSAID allergy and safe alternatives. Another strength of our study was that we performed a challenge with ASA or ibuprofen in the cases with a reaction to a single NSAID. Therefore, we had the chance to exclude the cross-reactive type of NSAID hypersensitivity in this group.

In conclusion, self-reported NSAID hypersensitivity reactions should be evaluated with a standardized diagnostic work-up. The existence of a reaction within an hour of drug intake, the presence of multiple NSAIDs hypersensitivity and family history of atopy are confirmed as significant risk factors for the development of NSAID hypersensitivity. Moreover, our study suggests that there are some patients with confirmed NSAID hypersensitivity who do not fit into the current classifications based on clinical manifestations and possible underlying diseases. Furthermore, multiple NSAID hypersensitivity may depend on not only COX-1 inhibition but also chemical structure or other unknown factors.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

TA is the first author of this manuscript. GA performed some part of allergy tests. DY performed the statistical analysis and interpretation of the results. SB critically revised the manuscript. SK designed the study, performed the interpretation of the results and revised the manuscript. All authors have read and approved the final manuscript.

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