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Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs in adults: Beyond current classification

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Abstract
Background: Hypersensitivity reactions (HSRs) to nonsteroidal anti-inflammatory drugs (NSAIDs) are a significant clinical issue. Several classifications have been proposed to categorize these reactions, including the current European Academy of Allergy and Clinical Immunology/European Network for Drug Allergy (EAACI/ENDA) classification. This study aimed to evaluate the applicability of this classification in a real-world clinical setting.
Methods: We conducted a national multicenter study involving patients from nine hospitals in four major urban centers in Turkey. All patients had a suggestive clinical history of hypersensitivity reactions to NSAIDs. Researchers collected data using a structured form and classified reactions based on the EAACI/ENDA classification. Oral provocation tests with several NSAIDs were performed using a single-blind challenge per EAACI/ENDA guidelines.
Results: Our retrospective study included 966 adult patients with a history of hypersensitivity to NSAIDs. The most common triggers were Acetylsalicylic Acid (ASA), paracetamol, and metamizole. The most prevalent acute NSAID hypersensitivity group was NSAID-induced urticaria/

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angioedema (NIUA) (34.3%). However, 17.3% of patients did not fit neatly into the current EAACI/ENDA classification. Notably, patients with underlying asthma or allergic rhinoconjunctivitis exhibited unusual reactions, such as urticaria and/or angioedema induced by multiple chemical groups of NSAIDs, blended mixed reactions, and isolated periorbital angioedema in response to multiple chemical groups of NSAIDs.
Conclusions: While the EAACI/ENDA classification system stratifies NSAID-induced hypersensitivity reactions into five distinct endotypes or phenotypes, it may not fully capture the diversity of these reactions. Our findings suggest a need for further research to refine this classification system and better accommodate patients with atypical presentations.

Introduction

Nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity reactions (HSRs) present a significant clinical challenge due to their diverse presentations and pathomechanisms.[1-3] Developing a comprehensive classification system has been challenging, with multiple classifications proposed in the literature.[4-10] This diversity in classifications can lead to confusion when interpreting the literature and comparing studies. The latest European Academy of Allergy and Clinical Immunology (EAACI) classification of NSAID hypersensitivity is widely accepted. It distinguishes between acute HSRs, which occur within hours of exposure, and late reactions occurring more than 24 h later.[6]

Acute HSRs are divided into four subgroups[6]:

1. NSAID: Exacerbated rhinitis and asthma in patients with underlying asthma, nasal polyps, and rhinosinusitis (N-ERD)
2. NSAID: Exacerbated Cutaneous Disease (NECD) in patients with underlying chronic urticaria (U) or angioedema (AE)
   Patients in these two groups react to all cyclooxygenase-1 (COX-1) inhibitors, suggesting COX-1 inhibition as an underlying mechanism.
3. NSAID: Induced urticaria/angioedema (NIUA) in otherwise healthy subjects without underlying chronic skin or respiratory disease. In this subgroup, the IgE-mediated mechanism seems unlikely because patients may react with entirely different chemical structures to NSAIDs. COX-1 inhibition has been suggested for this type of reaction.[6]
4. Single NSAID-induced urticaria, angioedema, or anaphylaxis (SNIUAA) are defined as HSRs to a single NSAID or several NSAIDs belonging to the same chemical group, manifesting as urticaria, angioedema, and anaphylaxis. These subjects tolerate other chemically nonrelated NSAIDs and do not have a history of chronic urticaria or asthma. SNIUAA can be IgE-dependent, where the drug acts as an allergen and triggers the immune system to produce specific IgE antibodies.

Delayed HSRs to NSAIDs are characterized as single NSAID-induced delayed hypersensitivity reactions (SNIDR) and usually appear within 24–72 h after drug administration.[6] SNIDR manifests by either skin symptoms (exanthema, fixed drug eruption [FDE]), other organ-specific symptoms (e.g., renal, pulmonary), or severe cutaneous adverse reactions (SCAR). The mechanism of SNIDR is thought to be T-cell-mediated, as opposed to IgE-mediated.[11]

Although the EAACI/ENDA classification provides evidence-based recommendations for managing hypersensitive patients, recent data suggest that certain patients cannot be classified into the phenotypes described by the EAACI/ENDA group, indicating critical unmet needs in understanding and managing NSAID hypersensitivity reactions.[9,12-15] This study aims to assess NSAID HSRs that do not fit the latest EAACI classification, focusing on potential new phenotypes and describing the culprit drugs in Turkey.

Material and Methods

In this retrospective, multicenter study, we used a structured form to collect data from patients with a history of hypersensitivity reactions (HSRs) to nonsteroidal anti-inflammatory drugs (NSAIDs). The form included patient demographics, coexisting allergic diseases, and details of the patient's history of hypersensitivity reactions to NSAIDs. This included the name of the culprit NSAID, the timing of the reaction, the number of HSRs experienced, symptoms, and information on the diagnostic approaches used. A total of 966 patients diagnosed with NSAID hypersensitivity based on clinical history, skin testing, and oral provocation testing (OPT) were included in the study. The patients included in this study were recruited over a 1-year period, from May 2017 to 2018, with a mean age of 40.9 ± 12.97 years.

Patients

Patients were retrospectively enrolled from nine hospitals in four Turkish cities (Istanbul, Ankara, Bursa, and Rize). Patients were classified into specific groups, such as NIUA, NECD, and N-ERD, based on their clinical history and hypersensitivity reactions to NSAIDs following the EAACI/ENDA classification system (6). Subjects with symptoms attributable to known side effects of NSAIDs were excluded.

Evaluation of atopy

Atopy was defined as a positive skin prick test (SPT) to at least one of the aeroallergens. We used the puncture

method, with a mean wheal diameter of 3 mm or greater than the negative control considered positive. The most common glycerinated extracts (ALK-Abello, Horsholm, Denmark) of the following allergenic sources were used in SPTs; *Dermatophagoides pteronyssinus and farinae,* grass, tree, weed pollens, cat and dog dander, *Alternaria alternata*, *Blattella germanica*, and Cladosporium antigens.

Oral provocation tests

The diagnosis of NSAID hypersensitivity was established through a comprehensive evaluation of the patient's medical history and an OPT using acetylsalicylic acid (ASA) or the suspected NSAID agent. The senior physician at each center decided to perform an OPT with ASA or the suspected NSAID agent based on their expertise and the guidelines available at the time of the study. Nonbronchial symptoms, such as ocular symptoms (e.g., redness, itching, and tearing), cutaneous symptoms (e.g., rash, hives, and angioedema), and gastric symptoms (e.g., abdominal pain, nausea, and vomiting) accompanying respiratory symptoms, were also considered indications of NSAID hypersensitivity.[6]

A single-blind oral provocation test with ASA was performed according to a previously described protocol,[16] administering consecutive doses of ASA at 90-min intervals, increasing to a total cumulative dose of 500 mg. The test was considered positive if at least a 20% reduction in forced expiratory volume in 1 s (FEV1) compared to baseline and if different bronchial symptoms appeared. Extrabronchial symptoms were also recorded. The provocative dose of oral ASA causing a 20% fall in FEV1 (PD20) was calculated. All OPTs, including those with other NSAIDs such as meloxicam, paracetamol, nimesulide, naproxen, metamizole, diclofenac, and flurbiprofen, were conducted in a hospital setting with emergency facilities and trained medical personnel. All OPTs with NSAIDs other than ASA were conducted following specific protocols and guidelines available during the study period for each drug. Due to variations in protocols across different centers and the individualized nature of the provocation doses, the exact details of these doses are not provided here. However, in all patients, the recommended daily dose of the drug was reached, ensuring adherence to standard practices. A positive history of NSAID hypersensitivity was defined as the onset of nasal congestion, rhinorrhea, shortness of breath, or rapidly progressing bronchial obstruction within hours of ingesting ASA or other COX-inhibiting NSAIDs.[6] In addition to respiratory symptoms, skin reactions such as rash, hives, and angioedema indicated NSAID hypersensitivity. Extrabronchial and cutaneous symptoms were recorded and evaluated as part of the overall hypersensitivity assessment. Skin prick and intradermal tests were performed using dilutions of meloxicam, paracetamol, nimesulide, metamizole, and diclofenac to assess skin reactions further. An OPT was considered positive in the same way for patients suspected of having hypersensitivity to other NSAIDs.

Ethics and statistical analysis

The study was approved by the Local Ethics Committee of Ankara University, School of Medicine, and written informed consent was obtained from all subjects (27 March 2017, 06-300-17). SPSS program v18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, with t-tests and chi-square tests applied to analyze differences in continuous and categorical variables. Results were evaluated at a $P < 0.05$ significance level.

Results

Characteristics of the study participants

The study enrolled 966 patients with a confirmed history of NSAID hypersensitivity, 34.6% (n = 264) identified as atopic. The demographic and clinical characteristics of the participants are detailed in Table 1. The most prevalent sensitivity was to house dust mites (n = 145, 54.9%). A significant number of patients reported concurrent allergic diseases, and over a quarter reported hypersensitivity to multiple chemical groups of NSAIDs. The three most common NSAIDs causing hypersensitivity reactions, as revealed by the patient's clinical history, were ASA, paracetamol, and metamizole, followed by flurbiprofen, naproxen, and diclofenac comprising 35,6% (n = 344), 33.4% (n = 323), 32.1% (n = 310), 28.4% (n = 274), 25% (n = 241), and 23.3% (n = 225), respectively. The average time between the ingestion of the culprit drug and the onset of the HSR was approximately 92.9 minutes (Relevant data were available in 535 patients).

Among the 375 patients tested for NSAID hypersensitivity, 156 patients (77.6%) were confirmed to have NSAID hypersensitivity based on the positive results of oral provocation tests (OPTs) and/or SPTs. Of the 201 patients who underwent OPT using aspirin (ASA), 137 (68.2%) exhibited a positive reaction. An additional 19 patients demonstrated a positive response when OPT was performed using a non-ASA NSAID. Among the 143 cases where a skin test was performed with the culprit NSAID, only 37 (25.8%) were

Table 1 Demographic and clinical characteristics of the study group.

Gender (female; n, %)	669 (69.2%)
Age (mean ± SD), years	40.9 ± 12.97
Atopy	264 (34.6%)
• *HDM*	145 (54.9%)
• *Pollen*	131 (49.6%)
• *Both*	42 (15.9%)
Underlying diseases	584 (69.3%)
• *Asthma*	234 (40.1%)
• *Allergic rhinitis*	159 (27.2%)
• *Chronic urticaria*	144 (24.7%)
• *Chronic rhinosinusitis with nasal polyps*	142 (14.7%)
Distribution of HSRs to NSAIDs by chemical group	
• *Single NSAID*	288 (29.8%)
• *Two NSAIDs*	349 (36.1%)
• *Three NSAIDs*	192 (19.9%)
• *>Three NSAIDs*	137 (14.2%)

HDM: house dust mite; HSR: hypersensitivity reactions; NSAID: nonsteroidal anti-inflammatory drug

positive. The prevalence of asthma and nasal polyposis history was significantly higher in the ASA OPT-positive group compared to the negative group, with rates of 51.8% versus 10.9% ($P < 0.001$) and 51.8% versus 3.1% ($P < 0.001$), respectively. The incidence of patients without any underlying chronic disease was significantly higher in the ASA OPT negative group compared to the ASA OPT positive group, with proportions of 64.4% and 19.7%, respectively ($p < 0.001$). The distribution of NSAID hypersensitivity testing results is shown in Figure 1.

Overall, the vast majority of (81.2%, $n = 784$) the patients were classified as having an acute drug reaction, only a few patients 1.6% ($n = 15$) reported a delayed-type reaction, whereas 17.3% ($n = 167$) did not meet any classification criteria, (Table 2). Of the delayed reaction group patients, 60% ($n = 9$) had fixed drug eruption (FDE). The remaining 40% had maculopapular drug eruption, and 46.7% of these patients reported the culprit NSAID as naproxen.

In the study, NSAID-induced urticaria/angioedema (NIUA, as defined in the introduction) was the most common acute NSAID hypersensitivity group, comprising 34.3% ($n = 269$) of the cases. NECD (NSAID-exacerbated cutaneous disease) was the least common, with 15.6% ($n = 122$) cases. Paracetamol was the most commonly reported culprit NSAID in both groups. Diclofenac was the most reported culprit NSAID in the SNIUAA group, and 30.6% of patients had a history of anaphylaxis. N-ERD was observed in 207 (26.4%) patients. Atopy incidence was higher in the N-ERD group (44%, $n = 68$) compared to other groups. Among the 207 N-ERD patients, 196 were further classified into subgroups based on clinical reaction type, including blended reaction ($n = 75$, 36.2%), upper and lower airway

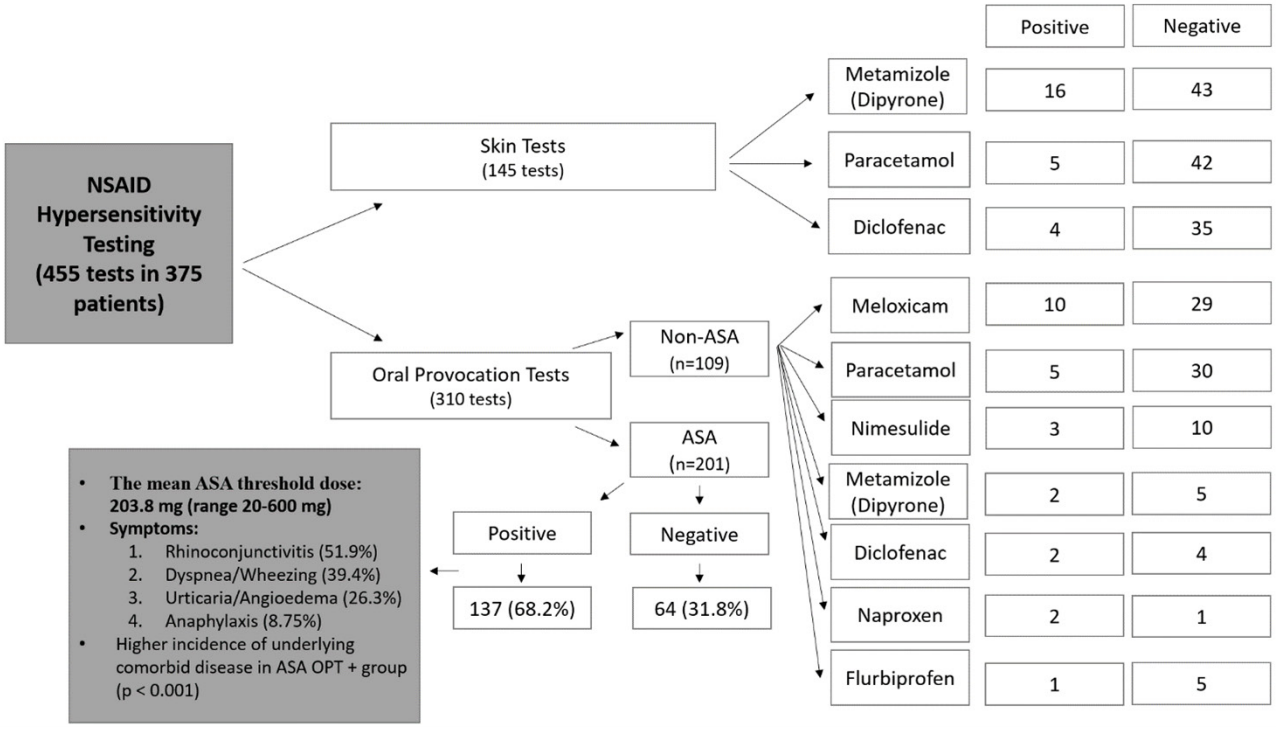

Figure 1 Overview of diagnostic tests for NSAID hypersensitivity.

Table 2 Classification of hypersensitivity reactions to NSAIDs.

	N/%	Gender (F/M)	Age (y) (Mean)	Atopy	Comorbid Disease	Culprit NSAID
Acute Rx.	784/81.2	538/246	41.1	173 (% 30.9)	1. Asthma 2. NP 3. Urticaria	1. ASA 2. Paracetamol 3. Metamizole
Unclassified Rx.	167/17.3	120/47	39.4	90 (% 66.1)	1. Sinusitis 2. Asthma 3. AR	1. Metamizole 2. ASA 3. Paracetamol
SNIDR	15/1.6	10/5	45.3	1 (% 10)	1. Urticaria 2. Drug allergy 3. Asthma	1. Naproxen 2. ASA 3. Meloxicam

AR: allergic rhinoconjunctivitis; ASA: Acetylsalicylic acid; F: Female; M: Male; NP: Nasal polyposis; NSAID: Nonsteroidal anti-inflammatory drug; Rx: Reaction; SNIDR: Single-NSAID-induced delayed hypersensitivity reactions; y: Years

reaction (n = 72, 34.8%), and only upper airway reaction (n = 49, 23.7%). Further details are presented in Table 3 and Figure 2.

Among the 966 patients with NSAID hypersensitivity, 167 patients (17.3%) could not be completely classified based on the current ENDA classification. These patients are categorized in Table 4. Of these 167 patients, the most reported culprit drug was metamizole (n = 66, 39.5%), followed by ASA (n = 61, 36.5%) and paracetamol (n = 55, 32.9%).

Discussion

Our study aimed to classify NSAID hypersensitivity reactions using the current classification system (6). We evaluated 966 patients with a history of HSRs to NSAIDs and found that 167 patients (17.3%) could not be entirely classified with this system. The current classification system for NSAID hypersensitivity includes non-immunologic HSRs (N-ERD, NECD, and NIUA) and immunologic HSRs (SNIUAA and SNIDR) with various clinical presentations from macular

Table 3 Classification of acute hypersensitivity reactions to NSAIDs according to the EAACI/ENDA.

	N/%	Gender (F/M)	Age (y) (Mean)	Atopy	Comorbid Disease	Culprit NSAID
NIUA	269/34.3	172/97	39.9	44 (24.7%)	None	1. Paracetamol 2. ASA 3. Metamizole
SNIUAA	186/23.7	137/49	44.4	30 (20.2%)	None	1. Diclofenac 2. Metamizole 3. Paracetamol
N-ERD	207/26.4	142/65	41.1	68 (%44)	1. Asthma 2. NP 3. AR	1. ASA 2. Metamizole 3. Flurbiprofen
NECD	122/15.6	87/35	39.1	31 (%34.4)	1. Urticaria	1. Paracetamol 2. Flurbiprofen 3. ASA

AR: allergic rhinoconjunctivitis; ASA: Acetylsalicylic acid; F: Female; M: Male; NP: Nasal polyposis; N-ERD: NSAIDs-exacerbated respiratory disease; NECD: NSAIDs-exacerbated cutaneous disease; NIUA: Multiple NSAID-induced urticaria/angioedema in otherwise healthy subjects; NSAID: Nonsteroidal anti-inflammatory drug; Rx: Reaction; SNIUAA: Single drug-induced urticaria/angioedema/anaphylaxis; y: Years

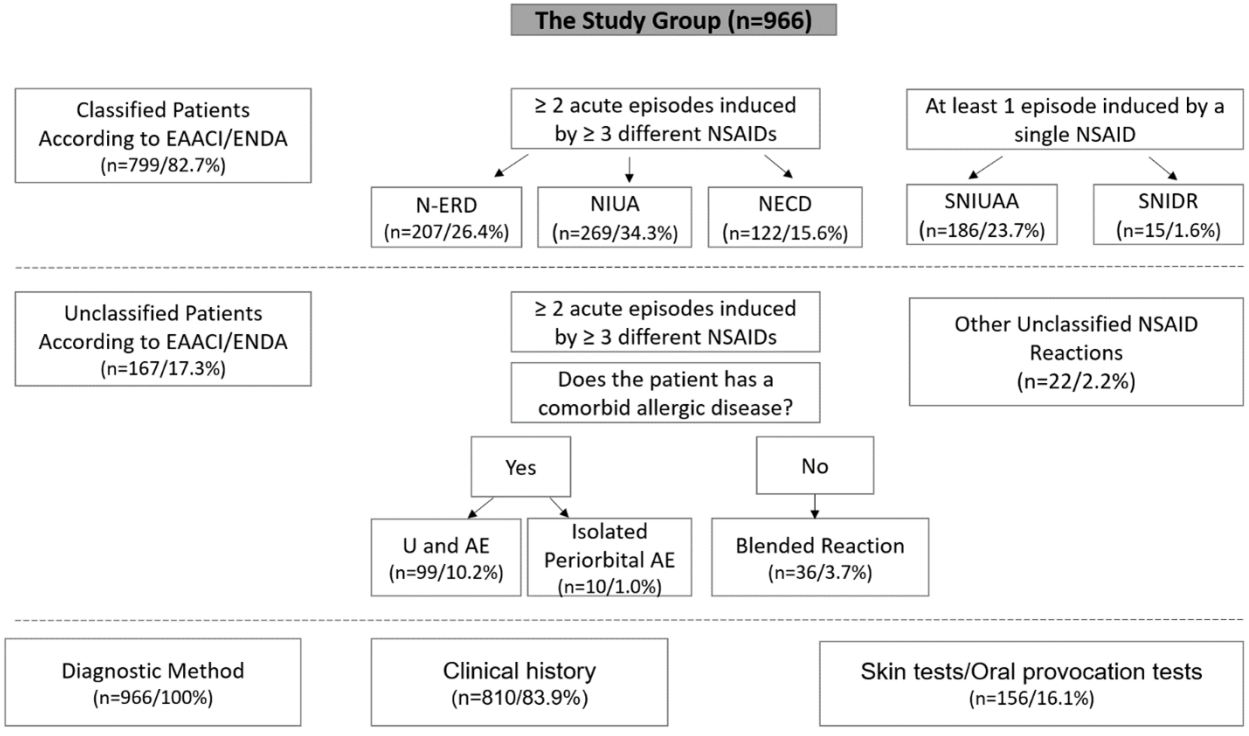

Figure 2 Classification of patients with hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) according to the EAACI/ENDA system.

Table 4 Categorization of unclassified patients according to the ENDA classification criteria.

Categories	N/%	Gender (F/M)	Age (Mean, y)	Culprit NSAID
U/AE with Asthma/AR/NP[a]	99/59.3	71/28	39.2	1. Metamizole 2. ASA 3. Paracetamol
Blended Systemic reaction[b]	36/21.6	22/14	40.2	1. Paracetamol 2. Metamizole 3. ASA
Isolated periorbital AE with AR/Asthma[c]	10/6	8/2	31.4	1. ASA 2. Metamizole 3. Paracetamol
Non-urticarial rash with AR/Asthma[d]	3/1.8	2/1	36	1. Paracetamol 2. Nimesulide
Single drug-induced asthma or AR[e]	1/0.6	1/-	62	1. Acemetazine
Naso-ocular reaction[f]	1/0.6	1/-	38	1. ASA 2. Naproxen
Unspecified[g]	17/10.1	15/2	43.5	1. Flurbiprofen 2. Paracetamol

AE: Angioedema; AR: Allergic rhinoconjunctivitis; ASA: Acetylsalicylic acid; F: Female; M: Male; NP: Nasal polyposis; NSAID: Nonsteroidal anti-inflammatory drug; U: Urticaria; y: Years; Rx: Reaction

[a] Urticaria or/and Angioedema due to multiple chemical groups of NSAIDs in patients with asthma and/or allergic rhinoconjunctivitis and/ or nasal polyposis.

[b] Blended systemic reaction due to multiple chemical groups of NSAIDs in patients without any comorbid chronic allergic diseases.

[c] Isolated periorbital angioedema due to multiple chemical groups of NSAIDs in patients with asthma or allergic rhinoconjunctivitis.

[d] Non-urticarial rash due to multiple chemical groups of NSAIDs in patients with asthma or allergic rhinoconjunctivitis.

[e] Asthma or allergic rhinoconjunctivitis symptoms due to a single chemical group of NSAIDs.

[g] Naso-ocular reaction due to multiple chemical groups of NSAIDs in patients without any comorbid chronic allergic diseases.

[h] Uncategorized patients due to all efforts.

eruption to SCAR. The reactions can involve COX-1 inhibition, IgE-mediated reaction, or Type IV immune mechanism and manifest as cutaneous or organ-specific symptoms (6).

In our analysis of NSAID hypersensitivity reactions, we have further elaborated on the evidence supporting the association between the identified phenotypes and pre-existing respiratory diseases, such as asthma, rhinitis, or polyposis. This relationship is distinct from the existing ENDA-EAACI classification, encompassing a broader spectrum of reactions. By examining the underlying mechanisms and clinical manifestations, we have provided a clearer understanding of this connection, enhancing our study's comprehensiveness. Our cohort identified a distinct phenotype characterized by urticaria and/or angioedema in response to multiple chemical groups of NSAIDs in patients with preexisting asthma, allergic rhinoconjunctivitis, or nasal polyposis. The resulting HSRs manifested with skin findings, suggesting that this phenotype differs from the EAACI/ENDA classification. Another characteristic was the development of HSRs with multiple chemical groups of NSAIDs. In a similar study, only one out of 149 patients could not be classified according to the EAACI/ENDA classification system.[17] This case involved a child without underlying disorders who developed urticaria after ASA. Although this was the only unclassified case in their cohort, the authors of that study commented on the challenge of classifying patients with the coexistence of chronic urticaria and underlying respiratory disease.

We also observed a distinct phenotype characterized by isolated periorbital angioedema in patients with underlying asthma or allergic rhinoconjunctivitis in response to multiple chemical groups of NSAIDs. Quiralte et al. previously described this condition in atopic patients, which was not included in the EAACI/ENDA classification.[18,19] According to the EAACI/ENDA classification, NIUA refers to urticaria and/or angioedema induced by at least two NSAIDs with different chemical structures, but only in otherwise healthy individuals. In this phenotype, our patients with underlying respiratory diseases without chronic urticaria and/or angioedema reported isolated periorbital angioedema in response to different NSAIDs. Notably, all patients exhibiting this phenotype were also sensitive to house dust mites.

In our cohort, three patients with asthma or allergic rhinoconjunctivitis developed a non-urticarial rash due to multiple chemical groups of NSAIDs. Although limited in number, we classified these patients as a distinct phenotype, as they did not fit the NIUA or NECD diagnostic criteria. The reactions may be related to COX-1 enzyme inhibition, but this is speculative and requires further investigation. Due to the multicenter nature of the study and limited information on these cases, including the absence of dermatological evidence, photographs, and biopsy results, findings should be interpreted with caution.

Another unclassified group included a 62-year-old female patient with hypersensitivity to house dust mites who developed asthma and rhinoconjunctivitis symptoms due to metamizole. OPTs for ASA and meloxicam were negative, while diclofenac elicited bronchospasm and nasal symptoms. The observed reaction to metamizole and lack of reaction to ASA in this patient is noteworthy and

inconsistent with typical response patterns. While bronchial hyperresponsiveness could be a potential explanation, this study did not specifically assess it. The underlying mechanisms for this specific reaction pattern may be complex and highlight the need for individualized assessment and consideration of multiple factors that could influence drug sensitivity. This case underscores the importance of continued research and exploration into NSAID hypersensitivity.

Additionally, one nonatopic patient without comorbid chronic allergic diseases experienced a nasoocular reaction due to multiple chemical groups of NSAIDs. Our investigation revealed a positive ASA OPT result in this patient. Although the mechanism may be related to COX-1 inhibition, the patient's clinical presentation did not fit the EAACI/ENDA classification.

Classifying patients can be challenging due to the diverse range of underlying medical conditions and reaction patterns. We classified 799 out of 966 (82.7%) patients with NSAID hypersensitivity according to the EAACI/ENDA classification. Other studies have reported similar challenges. One study analyzing 30 pediatric patients with NSAID hypersensitivity found that 16.7% (5 subjects) could not be classified according to the EAACI/ENDA classification.[20] The researchers concluded that NSAID hypersensitivity manifests differently in pediatric patients, and classification systems based on adult data may not be entirely applicable to all cases in this age group.

Caimmi et al. found that 16.9% (107 out of 635) of pediatric patients were diagnosed with NSAID hypersensitivity, but 40.2% (43 patients) could not be classified according to ENDA recommendations.[21] They suggested a modified classification scheme that disregards the potential presence of underlying chronic illnesses in pediatric patients. In a study involving 106 children, one patient with cross-intolerance could not be classified according to pathomechanisms, and seven patients with cross-intolerance could not be categorized based on the underlying disease and clinical manifestations using the EAACI/ENDA method.[12] It can be argued that the validity of these studies may be limited, as the ENDA classification primarily focuses on adult populations. This has led to some studies done in the adult population questioning the efficacy of the ENDA classification and even proposing alternative classification systems.

In a Danish study, Nissen et al. classified 38 out of 39 adult patients according to the EAACI/ENDA classification. The higher rate observed in their study may be attributed to the selection of patients based on OPT-positivity.[17] In their study of 308 adult patients with HSR to NSAIDs, Demir et al. found that the most prevalent subtype of NSAID hypersensitivity was NIUA, observed in 46.4% of subjects, while the least frequent subtype was SNIDR, observed in only 1.6% of subjects.[22] In comparison, our study found that the most common acute NSAID hypersensitivity subgroup was NIUA, with a frequency of 34.3%. However, unlike Demir et al., we classified more patients who did not meet the EAACI/ENDA criteria (17.3%). This discrepancy may be due to their inclusion of periorbital edema resulting from different chemical NSAIDs in atopic patients within the NIUA subgroup, while we considered it a distinct subtype. A Turkish study reported N-ERD as the most prevalent subgroup (32%) and SNIDR as the least frequent (1.5%), with only two patients (1.0%) not fitting the ENDA criteria.[10] The authors suggested a new classification to address the overlap between patient groups, serving as an alternative or supplement to the ENDA classification.

The blended reaction, which involves mixed reactions where patients experience both immediate skin and respiratory symptoms in response to different classes of NSAIDs, was identified as a specific phenotype that we observed but was not included in the EAACI/ENDA classification. This contrasts with the current classification system that considers NSAID-induced anaphylaxis IgE-mediated, and nonallergic anaphylaxis is not well-defined in the system. It is worth noting that blended reactions were reported in over 25% of all reactions induced by cross-reactivity to NSAIDs in adults in a large study by Doña et al.[23] Furthermore, we also observed this specific phenotype in our study but did not include it in the EAACI/ENDA classification. In the study by Demir et al., five patients (1.6%) were categorized as having blended reactions due to symptoms that did not fit into the established subgroups.[22] In contrast, in our study, the percentage of patients categorized as having blended reactions was lower than Doña et al. and higher than Demir et al. at 3.7%. This discrepancy may result from the absence of a widely recognized definition and variations in methodologies. In our study, paracetamol was the most commonly reported culprit NSAID in NIUA and NECD groups. It should be noted that in Turkey, paracetamol is one of the most frequently prescribed drugs. It is often found in combination with other substances. This widespread use and combination with other active ingredients may contribute to its prominence as our study's most commonly reported drug. This observation is particularly noteworthy considering paracetamol's general tolerability in patients with NIUA, NECD, or N-ERD. The complexity of these combinations and the unique prescribing patterns in our region may offer insights into the unexpected hypersensitivity reactions observed in our study population.

The diagnostic criteria for our study population included objective OPT in 16.1% of subjects, while 70.2% had a clinical history of HSRs to at least two chemically distinct NSAIDs. In total, 74.5% of subjects were diagnosed through more objective criteria, with the remaining 25.5% based on reliable clinical history and consistent symptom presentation.

While the retrospective design and each center deciding whether to include OPT in their diagnostic algorithms based on their local possibilities and expertise, resulting in the lack of OPT among all participating centers, were limitations of our study, it also possessed some strengths. All OPTs and SPTs followed established guidelines to ensure accuracy and reliability in detecting NSAID hypersensitivity. While we recognize that OPT and SPT are not equivalent in sensitivity and specificity, and those false positive/negative findings are possible, our methodology was designed to minimize these risks. The combination of OPT and SPT and careful consideration of patient history and symptoms comprehensively assessed NSAID hypersensitivity in our study population. Notably, this nationwide study involved the most extensive cohort regarding HSRs to NSAIDs. The study's authors were experts in diagnosing HSR with drugs, including NSAIDs.[1,24-29] In this regard, the authors focused on the patients' details, which could not be classified according to the currently defined ENDA criteria. The study was

based on a standardized questionnaire, which may have caused recall bias. The lack of biomarkers based on pathogenic mechanisms, such as urinary Leukotriene E4, serum periostin, and other inflammatory markers, limits our ability to classify these patients and provide new insights into this classification. We recognize that our study has certain limitations in determining the association between the identified phenotypes and preexisting respiratory diseases. The complexity of these reactions and the multifaceted nature of the underlying diseases may have contributed to the ambiguity in our initial findings. While our study lays the groundwork for understanding this association, further research, including controlled trials and longitudinal studies, may be needed to clarify these relationships more precisely. Overall, our findings contribute to a better understanding of the prevalence of different phenotypes of NSAID-induced HSRs in this population.

Conclusion

Our study has identified distinct phenotypes of NSAID hypersensitivity associated with preexisting respiratory diseases. We have elucidated this association, highlighting how it diverges from the current ENDA-EAACI classification. Despite the limitations in our methodology, our findings contribute to a more nuanced understanding of NSAID hypersensitivity. This research underscores the importance of individualized assessment and consideration of multiple factors that could influence drug sensitivity, paving the way for more targeted therapeutic approaches. We hope our research could assist allergists in better understanding the HSRs to NSAIDs and suggest a possible modification to the current classification.

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Conflicts of interest

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