Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

A new classification option for NSAID hypersensitivity: Kalyoncu classification

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Received 5 June 2022; Accepted 28 July 2022
Available online 1 November 2022

KEYWORDS
drug hypersensitivity; European Network for Drug Allergy; Kalyoncu classification; nonsteroidal anti-inflammatory drugs

Abstract
Background: The European Network for Drug Allergy (ENDA) proposed a consensus document for hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) in 2011. A subgroup of patients with NSAIDs-exacerbated respiratory disease (NERD) develop urticaria/angioedema type reactions in response to NSAIDs. The Kalyoncu classification might be a novel option to classify patients with NSAID hypersensitivity (NH). In this study, we compare the ENDA and the Kalyoncu classifications.
Methods: This study enrolled a total of 196 patients. NH reaction types were categorized as asthma, rhinitis, urticaria/angioedema and anaphylaxis. Based on the reaction history and oral provocation test findings, patients were grouped according to ENDA and Kalyoncu classifications.
Results: The mean age of the 196 patients was 40.32±13.28 years, and 130 (66.3%) of them were female. Under the ENDA and Kalyoncu classifications, the most common NH subgroups were NERD (32%), and isolated NH (34.2%), the least prevalent NH subgroups were single NSAID-induced delayed reactions (SNIDR) (1.5%), and pseudo Samter's syndrome (11.7%).
Conclusions: Our research revealed that the Kalyoncu classification is more descriptive of patients with NERD exhibiting urticaria/angioedema-type reactions. It also provides future risk assessment for development of NERD. For controversial cases, the Kalyoncu classification can be utilized as a new complimentary option alone or in conjunction with ENDA classification.

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https://doi.org/10.15586/aei.v50i6.693

Introduction

Acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly implicated medications in hypersensitivity reactions to drugs.[1-3] The reactions mediated by specific immunologic mechanisms are defined as allergic reactions, and when the reactions mediated by non-immunologic mechanisms (cyclooxygenase-1 inhibition or cross-reactive or cross-intolerance) these are defined as "non-allergic hypersensitivity".[4] Hypersensitivity reactions manifest as various symptoms related to the skin (rash, urticaria (u), and angioedema (ae)) and the respiratory tract (rhinorrhea, nasal congestion, bronchial obstruction, and dyspnea); even anaphylaxis may emerge in some cases.[5-6] In 2011, the European Academy of Allergy and Clinical Immunology Interest Group on Drug Allergy/European Network for Drug Allergy (EAACI/ENDA) suggested a consensus paper that includes the definitions and classifications of hypersensitivity reactions to NSAIDs and practical algorithms for their diagnosis and management.[5] The ENDA classification has been a useful reference guide for clinicians and investigators working in this field. The currently used classification was established in 2013 by a panel of experts from the European Academy of Allergy and Clinical Immunology Task Force on NSAIDs.[6] In this task force, the terminology for this classification system was revised to include NSAID-exacerbated cutaneous disease (NECD), NSAID-exacerbated respiratory disease (NERD), NSAID-induced u/ae (NIUA), single NSAID-induced u/ae and anaphylaxis (SNIUAA), and single NSAID-induced delayed reactions (SNIDR). The first three classes comprise cross reactor patients (patients that have hypersensitivity to all potent COX enzyme inhibitors), while the last two are selective reactor patients (patients that have hypersensitivity to a single NSAID). However, some authors observed that numerous patients did not fit into only one category of ENDA classification.[7-11] Blanca Lopez et al. reported in a review that there are two additional groups that include selective NSAID-induced organ specific reactions (hepatitis, bile duct syndrome, and meningitis), and selective NSAID-induced skin/systemic manifestations (vasculitis).[12] Patients with NSAID cross-reactive anaphylaxis were described by Vasquez et al.[13] In a review, three different phenotypes beyond the ENDA classification were mentioned: blended reactions (cases of cross reactors affecting both the skin and the airways, as well as other organs)[3,7,14]; food-dependent NSAID-induced anaphylaxis[15-18] and NSAIDs-multiple selective immediate reactions (some cases may have immediate reactions to many NSAIDs but tolerate ASA).[19,20]

Rising data shows that NERD is heterogeneous in terms of the order of developing symptoms, pathogenetic mechanisms involved, and type of NSAID hypersensitivity (NH) reaction (e.g., respiratory, cutaneous, and gastrointestinal symptoms).[21] A Polish research identified four NERD phenotypes with distinct clinical features.[22] Also, a Korean research revealed four phenotypes of NERD.[23] A further study showed a number of cases with asthma and rhinitis who had respiratory reactions to a single NSAID (including paracetamol) but tolerated aspirin well.[10] Heterogeneity of NERD phenotypes has also been observed in children.[24] Therefore, one subgroup may not adequately describe all patients. In order to determine specific phenotypes, Karakaya et al. investigated the association between NH and chronic urticaria, rhinitis/rhinosinusitis, and asthma in NH patients and suggested a new classification system, namely, the Kalyoncu classification, wherein patients were classified under Samter's syndrome (NERD), pseudo-Samter's syndrome, incomplete Samter's syndrome, and isolated NH.[25] Samter's syndrome was defined as an NSAID-induced respiratory disease and pseudo-Samter's syndrome was defined as an NSAID-induced u/ae in patients with asthma. Incomplete Samter's syndrome comprises more than one subclasses defined as 1) NH and rhinitis/rhinosinusitis/nasal polyposis; 2) asthma or rhinitis/rhinosinusitis/nasal polyposis and a first-degree relative with NH/Samter's syndrome; 3) asthma, nasal polyposis, and rhinitis/rhinosinusitis; and 4) NH and a first-degree relative with Samter's syndrome/asthma/rhinitis/rhinosinusitis/nasal polyposis (Figure 1). As observed from the definitions, family history was important in the categorization of patients according to the Kalyoncu classification.

The Kalyoncu classification was originally developed to create a risk analysis of developing Samter's syndrome (NERD) over time in patients who were prone to develop Samter's syndrome. This study compared the Kalyoncu and the ENDA classifications with each other, especially for patients with NERD.

Methods

The study was performed at the Hacettepe University Hospital, Department of Chest Diseases, Division of Allergy and Clinical Immunology. In this cross-sectional research 195 patients with NH confirmed by clinical history or drug provocation tests, and one patient with asthma, rhinitis, and nasal polyposis who had a sister with NH were included (total of 196 patients). The demographic features, clinical characteristics, and duration of hypersensitivity reactions, tolerated NSAIDs, concomitant disorders (rhinitis/rhinosinusitis, asthma, nasal polyposis, chronic urticaria, atopic dermatitis, and additional antibiotic/venom/food allergy) and age of onset of these diseases were recorded. Family history of drug allergies, chronic urticaria, NH, and asthma were evaluated. The following categories of NH reaction types were formed based on every patient's history: asthma, rhinitis, u, ae, and anaphylaxis. The diagnoses of rhinitis and asthma were established based on the Allergic Rhinitis and Their Impacts on Asthma and the Global Initiative for Asthma guidelines respectively, and chronic urticaria was described as spontaneous wheals and/or ae lasting >6 weeks.[26-28] Anaphylaxis was described as a severe and potentially fatal systemic hypersensitivity reaction characterized by a sudden onset of respiratory or cardiovascular symptoms.[29] Confirmation of NH was made according to reliable clinical history (≥2 reactions with the same or unrelated NSAIDs) and/or single-blind oral provocation tests (SBOPT). SBOPTs were used to verify the presence of NH and/or to find alternative analgesics. Each patient fulfilled the indication parameters for drug provocation testing recommended by ENDA.[6]

The ENDA and Kalyoncu classifications were made according to each patient's history and SBOPT results.

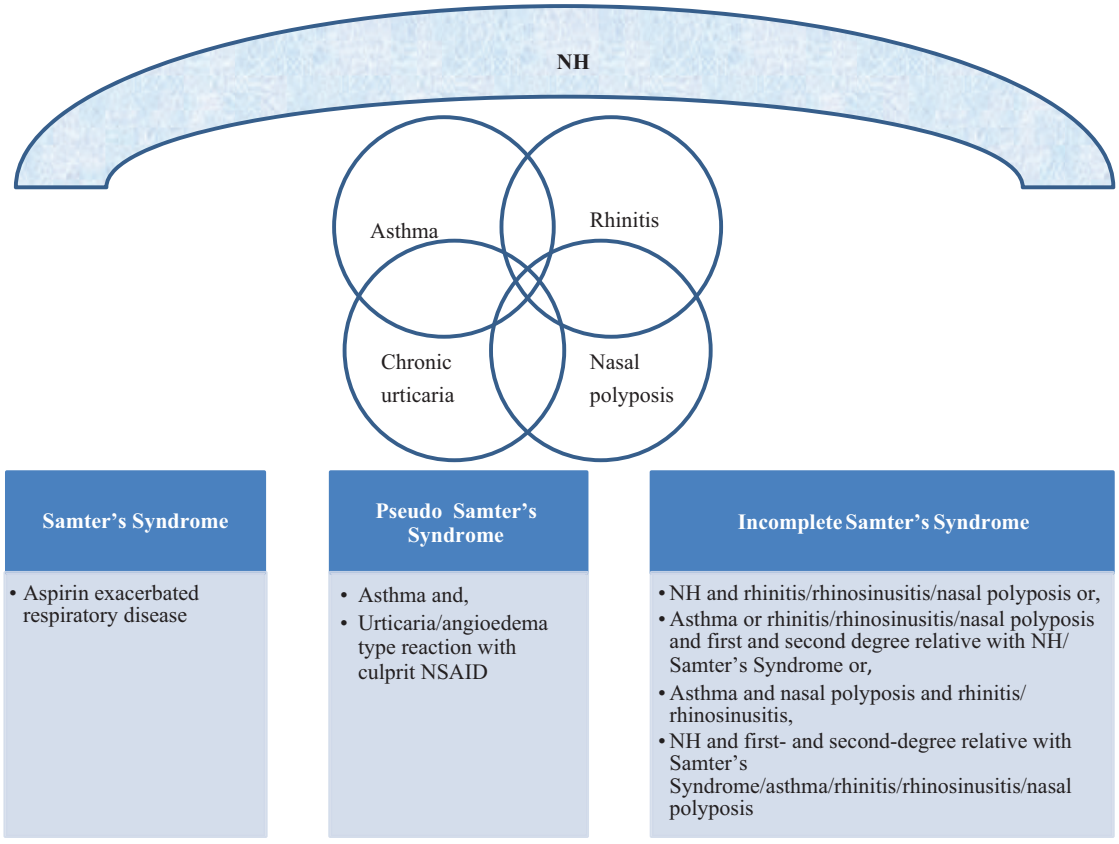

Figure 1 Classification scheme for Samter's syndrome (the Kalyoncu classification). NH, NSAID hypersensitivity.

This study was approved by the ethical committee of the Hacettepe University, and written informed consent was obtained from all patients. (GO 14/493-15)

Statistical analysis

The statistical program IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The results for continuous variables were presented as mean±SD; skewed distributions were presented as medians with IQRs.

Results

The study enrolled 196 patients who have visited our outpatient allergy clinic. Of the 196 patients, 130 were female (66.3%) and the mean age was 40.32±13.28 years. The demographical and clinical features of the patients are shown in (Table 1). The distribution of patients in terms of the ENDA and Kalyoncu classifications are displayed in (Tables 2 and 3). The most and least common NH subgroups were NERD (32%) and SNIDR (1.5%) in the ENDA classification, and NH (34.2%) and pseudo-Samter's syndrome (11.7%) in the Kalyoncu classification, respectively. A patient with asthma, rhinitis, and nasal polyposis who had a sister with NH was categorized as having incomplete Samter's syndrome, and another patient with respiratory symptoms induced by NSAIDs without accompanying asthma was categorized as NH according to the Kalyoncu classification. However, these two patients did not fit into any of the subgroups according to the ENDA classification.

It was shown that 24 patients included in the NERD subgroup, in addition to respiratory reaction, also exhibited

Table 1 Demographic and clinical features of patients.

Gender (female; *n*, %)	130 (66.3)
Age in years (mean±SD)	40.32±13.28
Ever smokers (*n*, %)	101 (52.9)
Presence of nasal polyposis (*n*, %)	41 (20.9)
SBOPT with ASA (*n*, %)	35 (17.9)
Accompanying diseases (*n*, %)	
Asthma	80 (40.8)
Chronic urticaria	31 (15.8)
PR	84 (42.9)
Additional allergic diseases (*n*, %)	
Antibiotic allergy	39 (19.9)
Food allergy	28 (14.3)
Venom allergy	9 (4.6)
AD	7 (3.6)
Age of onset of NH in years (mean±SD)	34.75±13.11
NH duration [years; median (min-max)]	3 (1-36)
Asthma duration [years; median (min-max)]	6 (1-30)
PR duration [years; median (min-max)]	7 (1-50)

SBOPT: single-blind oral provocation tests; ASA: acetylsalicylic acid; AD: atopic dermatitis; PR: persistent rhinitis; NH: nonsteroidal anti-inflammatory drug hypersensitivity.

Table 2 Distribution of patients according to ENDA classification.

	n (%)
NSAID-exacerbated respiratory disease (NERD)	62 (32)
NSAID-induced u/ae (NIUA)	54 (27.8)
Single NSAID-induced u/ae and/or anaphylaxis (SNIUAA)	53 (27.3)
NSAID-exacerbated cutaneous disease (NECD)	22 (11.3)
Single NSAID-induced delayed reactions (SNIDR)	3 (1.5)
Total patients	194* (100)

u/ae: urticaria/angioedema.
*Two patients could not be classified according to ENDA classification.

Table 3 Distribution of patients according to Kalyoncu classification.

	n (%)
Samter's syndrome	59 (30.1)
Incomplete Samter's syndrome	47 (24.0)
Pseudo-Samter's syndrome	23 (11.7)
NSAID hypersensitivity (NH)	67 (34.2)
Total patients	196 (100)

u/ae-type reaction induced by different NSAIDs. Furthermore, two patients with NECD (patients with a history of chronic spontaneous urticaria who developed an exacerbation of urticaria after NSAID intake) were also experiencing respiratory reaction in response to different NSAIDs.

We observed that 8 (13.5%) of the 59 patients categorized as Samter's syndrome (NERD) according to the Kalyoncu classification tolerated ASA; however, a single NSAID caused a respiratory reaction without a cutaneous reaction in these patients.

Based on the detailed history of the 56 patients with a current diagnosis of Samter's syndrome (NERD), we observed that the initiation of symptoms was in the form of incomplete Samter's syndrome in 21 (37.5%), and as pseudo-Samter's syndrome in three (5.35%) patients. The remaining 32 patients were initially classified with Samter's syndrome. In patients with incomplete Samter's syndrome after a median time of 4 years (1-14), development of Samter's syndrome (NERD) was observed. In one patient, incomplete Samter's syndrome was diagnosed first that later presented as pseudo-Samter's syndrome. Later in the course, this patient was categorized to have Samter's syndrome (NERD). In three patients with a diagnosis of pseudo-Samter's syndrome after 6 months to 3 years, development of Samter's syndrome (NERD) was observed as the reactions changed from u/ae to the respiratory type.

In our previous study, only first-degree relatives having NH, asthma, or nasal polyposis were considered.[25] In this study, when second-degree relatives were taken into account, additional 11 patients were classified with incomplete Samter's syndrome. Family history of patients distributed according to the Kalyoncu classification is shown in (Table 4).

Discussion

ASA and NSAIDs are among the most frequently recommended drugs. They are responsible for up to 25% of all documented adverse drug events. These reactions manifest as immunologic and non-immunologic hypersensitivity reactions, and affect roughly 0.6%–2.5% of the general population.[9] However, its frequency in high-risk populations like the ones with asthma and nasal polyps, and chronic spontaneous urticaria rises to 20 and 30% respectively.[30] Classification of reaction patterns is important both for scientific and prognostic reasons. An appropriate and practical classification of NH reactions can help clinicians confirm the diagnosis, manage the disease, and determine a prognosis. In the literature, there are many published classification schemes that use several different criteria for the clinical classification of the reactions induced by NSAIDs.[3,5,7,31-33] However, the reaction pattern of a patient may change over time. It is possible that the first episode of NSAID-induced urticaria may be followed by onset of chronic urticaria some years later.[34] Similarly, a group of patients without asthma initially present with a rhinitis/asthma-type reaction to NSAIDs and subsequently have asthma that further progresses to NERD.[35]

NERD is one of the most problematic and well-known conditions related to deteriorating respiratory tract symptoms after the intake of ASA and other NSAIDs.[36] This disease is typically characterized by a natural sequence of symptoms. Rhinitis is present in most patients and is similar to a flu-like infection, then developing into perennial eosinophilic rhinosinusitis and nasal polyposis, followed by NSAID-induced respiratory reactions. However, it is not unusual for all symptoms to develop simultaneously. The onset of NERD typically occurs in the third or fourth decade of life, although NH may develop at any stage of

Table 4 Family history of patients according to the Kalyoncu classification.

	n	First- and second-degree relatives with asthma *n* (%)	First- and second-degree relatives with NH *n* (%)	First- and second-degree relatives with nasal polyposis *n* (%)
Samter's syndrome	59	30 (50.8)	7 (11.9)	2 (3.4)
Incomplete Samter's syndrome	47	29 (61.7)	7 (14.9)	1 (2.1)
Pseudo-Samter's syndrome	23	9 (39.1)	3 (13)	2 (8.7)
NSAID hypersensitivity (NH)	67	1 (1.5)	10 (14.9)	—

NH: nonsteroidal anti-inflammatory drug hypersensitivity.

the disease.[37] We have suggested a classification scheme for Samter's syndrome (the Kalyoncu classification).[25,33,38] We evaluated 1137 patients with NH and reported that 26.4% of the patients with asthma had NSAID-induced u/ae and were classified as having pseudo-Samter's syndrome.[25] Cahill et al. reported that a group of patients with NERD, after intake of aspirin had pruritic and erythematous cutaneous rash on their distal upper and lower limbs.[39] This reaction frequently occurred in relation with gastrointestinal symptoms, clinically different from those typically seen in NSAID-induced urticaria. According to the Kalyoncu classification, incomplete or pseudo Samter's syndrome may progress to Samter's syndrome overtime.

We previously reported that having a first-degree relative with NH/Samter's syndrome/asthma/rhinitis/rhinosinusitis/nasal polyposis was a risk factor for developing Samter's syndrome.[25] In this study, we also report the importance of NH/Samter's syndrome/asthma/rhinitis/rhinosinusitis/nasal polyposis in second-degree relatives. The involvement of familial history (genetic heritage) in the Kalyoncu classification may also provide projections and risk analysis for the future. If a patient with persistent rhinitis and nasal polyposis has a first-degree relative with the diagnosis of Samter's syndrome (NERD), they may be considered to have a higher risk of developing NERD in the future. In this study, we reported that patients in the incomplete Samter's syndrome group commonly had a first- and/or a second-degree relative with asthma (61.7%) and/or NH (4.9%). A previous study suggested that family history of ASA hypersensitivity, chronic rhinitis, and nasal polyposis were independent predictors for NERD.[40] Similar to family history, some environmental factors such as smoking, having a pet, and occupation may also affect the development of asthma and may have an impact on the transition between groups. The presence of preventable risk factors that may have a role in development of NERD should be investigated in future studies.

According to the ENDA classification, the NECD, NIUA, and SNIUAA subgroups of patients also experience asthma/rhinitis-type hypersensitivity reactions or have accompanying asthma/rhinitis. Likewise, the NERD subgroup of patients also experience u/ae-type hypersensitivity reaction or have accompanying chronic urticaria. Therefore, in the same patient, one NSAID may induce respiratory and another NSAID may induce u/ae-type reaction. Only one subgroup under the ENDA classification was not sufficient to describe some patients. It is difficult to express this issue using the ENDA classification. We observed five patients with features of more than one subgroup or who did not fit into any category under the ENDA classification. This problem has also been noted in previous studies.[7-13] Vally et al. reported an interesting group of non-asthmatic patients with respiratory symptoms induced by aspirin, similar to one patient in our study who could not be categorized using the ENDA classification.[41] We think that our classification is important, because a patient with asthma and an u/ae-type reaction to NSAIDs would not benefit from aspirin desensitization, or their asthma would be better controlled compared to those who experience an asthmatic-type reaction. This should also be further investigated.

In conclusion, some patients may have features of more than one subgroup according to the ENDA classification. Because there is some degree of overlap between the groups, the categorization of some patients may be difficult. For controversial cases and to understand clinical course and prognosis of the disease, the Kalyoncu classification can be used as a new or complementary option with the ENDA classification. Natural course of incomplete and pseudo-Samter's syndrome cases should be investigated further, which should also consider the family background.

Conflict of Interest

The authors declare no potential conflicts of interests with respect to research, authorship and/or publication of this article.

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