

CORRESPONDENCE

# A phenotype-based classification of NSAIDs hypersensitivity: new patients, new challenges

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NSAIDs hypersensitivity (NH) reactions are complex diseases which can be classified according to the clinical syndrome that occurred during single-blind placebo-controlled oral challenge (SBPCOC), the cross-reactive status among different cyclooxygenase inhibitors, and the existence of concomitant diseases (1). In the document prepared by the European Academy of Allergy and Clinical Immunology Task Force on NSAIDs Hypersensitivity (EAACI-TFNH), these same criteria have aided to delineate and propose the main subsets of NH (2). However, it seems reasonable to think that further clinical observations may define new entities. We propose to add to this new NH classification a distinct form of well-defined NH phenotype.

We agree with Kowalski and coworkers that NH is a broad group of disorders with distinct clinical and biologic characteristics which can be included in, at least, five types of reactions (2). In 2007, we evaluated the clinical features of SBPCOC carried out in a cohort of patients with NH, which supported a comprehensive phenotype-based classification of NH (1). Our findings also suggested that some patients described (1) may have certain clinical characteristics that

distinguish them as a distinct entity known as isolated periorbital angioedema (1, 3).

This NH phenotype was commonly seen in pediatric and juvenile patients (1, 3); most of them exhibited cross-sensitivity with other NSAIDs (1); and an underlying allergic respiratory disease was always present (mainly caused by house dust mites) (1, 3). Whether atopy or specific responses to certain allergens may predispose patients to some NH syndromes is largely unknown. Closely related with this reaction, we have also described a syndrome characterized by severe systemic reactions caused by ingestion of flour-based foods, contaminated with mites (the NSAIDs sensitivity mite ingestion reaction syndrome) (4). By controlled oral challenges, it was confirmed not only that the reactions were due to mite ingestion, but also that most patients showed isolated periorbital angioedema. It was estimated that the relative risk of atopic patients with NH for suffering a mite ingestion reaction was 300 times higher than that observed in NSAID-tolerant patients (5).

Recently, we realized a nasal ketorolac challenge (NKC) to three patients, who previously presented SBPCOC-proven isolated periorbital angioedema. Nasal airway and lower

**Table 1.** Challenge results of the patients with NSAID-induced periorbital angioedema

|                                                                 | Patient 1                                              | Patient 2                    | Patient 3                                                   |
|-----------------------------------------------------------------|--------------------------------------------------------|------------------------------|-------------------------------------------------------------|
| Age (in years)/sex                                              | 19/male                                                | 30/male                      | 56/female                                                   |
| Allergic respiratory disease                                    | Rhinitis and asthma/Alternaria                         | Rhinitis/mite, Alternaria    | Rhinitis and asthma/mite, olive pollen                      |
| SBPCOC                                                          |                                                        |                              |                                                             |
| Drug/dose                                                       | Diclofenac/50 mg                                       | Ibuprofen/600 mg             | Diclofenac/50 mg                                            |
| Elapsed time                                                    | 20 min                                                 | 30 min                       | 30 min                                                      |
| Clinical reaction                                               | Bilateral periorbital angioedema                       | Right periorbital angioedema | Bilateral periorbital angioedema                            |
| NKC                                                             |                                                        |                              |                                                             |
| Dose                                                            | 13 mg                                                  | 13 mg                        | 13 mg                                                       |
| Elapsed time                                                    | 40 min                                                 | 50 min                       | 80 min                                                      |
| Clinical reaction                                               | Left periorbital angioedema and conjunctival injection | Right periorbital angioedema | Bilateral periorbital angioedema and conjunctival injection |
| Sum of basal Vol 2–8 (in cm <sup>3</sup> ) in both nostrils     | 18.05                                                  | 16.15                        | 21.05                                                       |
| Sum of placebo Vol 2–8 (in cm <sup>3</sup> ) in both nostrils   | 19.23                                                  | 17.04                        | 20.96                                                       |
| Sum of Vol 2–8 (in cm <sup>3</sup> ) after NKC in both nostrils | 18.85                                                  | 18.02                        | 23.07                                                       |

SBPCOC, single-blind placebo-controlled oral challenge; NKC, nasal ketorolac challenge.

respiratory function was also evaluated in all patients during NKC using an acoustic rhinometer and a spirometer (Dato-spir, Sibelmed Lab, Spain), complying with the ERS recommendation. SBPCOC procedures were performed as previously described (1). A minimum 7-day period after a positive SBPCOC was deemed necessary before the NKC was realized in the same patient.

An initial single-blind challenge with saline as placebo was carried out to rule out a nasal hyperreactivity. If the sum of the volumes of both nasal cavities 2–8 cm from the nostril (Vol 2–8) after saline declined lower than 25%, patients underwent nasal challenge with 13 mg of ketorolac (Laboratorios Vita, Spain) administered by spraying between both nostrils (6).

Table 1 summarizes the clinical characteristics of SBPCOC and NKC reactions and the changes in Vol 2–8 during NKC procedure. All patients showed a positive skin reaction characterized by bilateral or unilateral angioedema between 30 and 90 min after nasal challenge. However, spirometry and acoustic rhinometric assessment was made during reactions without any significant changes.

In conclusion, our cohort clinical data (1, 3) and the abovementioned challenge results suggest that isolated periorbital angioedema could be included in the EAACI-TFNH classification as a distinct cross-reactive NH phenotype which affects younger atopic populations with mite allergic respiratory disease. Acoustic rhinometry may be an alternative method for identifying some patients who have isolated periorbital angioedema. This procedure induced milder reactions than SBPCOC in some patients and would help to rule out those frequent patients with blended skin and respiratory reactions found in the clinical practice.

### Conflicts of interest

The authors declare no conflicts of interest.

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### REPLY

We thank Quirarte et al. for their interesting correspondence addressing the heterogeneity of NSAID-induced hypersensitivity reactions and suggesting modification of the classification proposed by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force (1). Cases of isolated periorbital oedema (IPO) induced by aspirin or other NSAIDs have been reported both in children and in adults for several decades (2), and more recently in observational or challenge studies, IPO was found to be a common clinical presentation of the cutaneous form of NSAIDs hypersensitivity (3, 4). Accordingly, IPO was well known and considered by the expert panel, when the current classification was proposed. Classification of NSAIDs hypersensitivity reactions is based on timing, clinical pattern of symptoms and presence or absence of cross-reactivity with other, chemically nonrelated NSAIDs (5). An additional criterion is the presence or absence of underlying chronic disease of the skin or

respiratory tract, which may be helpful to diagnose some (cross-reactive type), but not other (single-drug-induced type) reactions (6). Because patients with IPO react to more than one, chemically nonrelated NSAIDs (thus presenting the cross-reactive type of hypersensitivity) and usually do not have underlying chronic cutaneous disease (chronic urticaria), they are considered to belong to the ‘multiple drug-induced urticaria and angioedema’ (5) or according to more recent nomenclature to the ‘NSAID-induced urticaria angioedema’ (NIUA) subtype (1). As opposed to earlier studies, more recent studies have documented that the presence of atopic diseases (rhinitis, asthma) and positive immediate-type skin tests to inhalant allergens are in fact quite common among patients with cross-reactive NSAIDs hypersensitivity [up to 80% of patients with NSAID-induced respiratory disease (NERD) and up to 60% with NIUA might be atopic] (1, 7). Interestingly, Doña et al. (7) found a significant association

between sensitization to mite allergens (*Dermatophagoides farinae* and *pteronyssinus*) and the NIUA type of hypersensitivity, which is consistent with common sensitization to house dust mites found among patients with NSAID-induced IPO. Thus, in our opinion, distinctive features of IPO (local manifestation and coexistence with house dust mite sensitivity) are not unique enough to justify separation of these patients from the NIUA type of hypersensitivity.

The letter of Quiralte et al. raises an important issue of at which point can the observations of a single study, even involving a significant number of patients challenged with a drug, be generalized and serve as a basis for the modification of an already existing classification? In fact, several challenge studies have reported a variable spectrum of manifestations of NSAID-induced hypersensitivity reactions, reflecting probably specific patients' local population (3, 4, 8), and accordingly, several modifications of classification have been proposed. In our opinion, the EAACI classification, which has been developed by a group of experts, includes the majority of observable NSAID-induced reactions and, on the other hand, is simple enough to be useful in clinical practice. We agree that the current classification is not final and should be refined and modified in future as long as our

knowledge on clinical presentations (e.g. not well-defined blended reactions) and on pathogenesis expands.

Quiralte et al. also present three patients with a history of IPO induced by diclofenac or ibuprofen, who developed periorbital angioedema and conjunctival injection after intranasal challenge with ketorolac, a nonselective NSAID. These observations seem to confirm the cross-reactive character of IPO and are consistent with previous reporting of systemic reactions (rhinitis and urticaria) to inhaled lysine aspirin challenge observed in patients with NERD (9), suggesting that absorption of NSAIDs from the airway mucosa (either nasal or bronchial) into the systemic circulation may lead to hypersensitivity reaction in another organ.

### Conflicts of interest

The authors declare no conflicts of interest.

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