Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Hypersensitivity Phenotypes: Don't Mislabel the NSAIDs-Augmented Food Allergy

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Introduction

- Adverse Drug Reactions (ADRs) are common and notable public health problem. It can be differentiated into two major subtypes: type A and B, as proposed by Rawlins and Thomson (Figure 1).
- NSAIDs are the most consumed drugs worldwide as the first line medication in many diseases but may also cause hypersensitivity reactions in susceptible individuals.
- There are many proposed classifications of NSAIDs hypersensitivity(NHS) which are based on the timing of the reactions, cross intolerance (CI), underlying disease and clinical patterns of reactions (respiratory, cutaneous, systemic, overlapping (blended) and/or organ specific).
- In 2013, the European Academy of Allergy and Clinical Immunology Task Force on NHS has proposed a refined classification and diagnosis with management approach of NHS – ENDA NHS guideline (Figure 2).

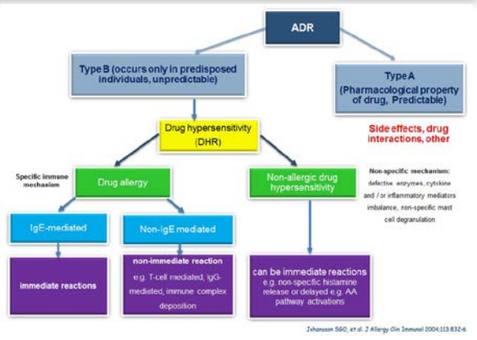

Figure 1. Definition and classification of adverse drug reactions

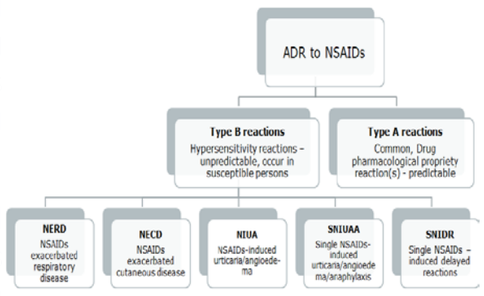

Figure 2. NSAIDs hypersensitivity classification by European Network for Drug Allergy, 2013

Objectives

- We investigated the NSAIDs hypersensitivity phenotypes involved, the clinical characteristics and, whether food allergy played a role.

Materials & Methods

- Sixty-five patients referred for NSAIDs hypersensitivity from 2016 to 2019 were recruited.
- Details of atopic status (defined as sensitization to at least one common environmental/food allergen with associated symptoms), symptoms manifestation, underlying disease associated with NSAIDs hypersensitivity and the NSAID(s) causing the reaction(s) were recorded and analyzed. Overlapping symptom was defined as CI with respiratory and cutaneous involvement or CI with anaphylaxis-like reaction or CI with delayed reactions.
- DP to a selective cyclo-oxygenase (COX) 2 inhibitor was performed for known CI patients and to a strong non-selective COX inhibitor if this is not known.
- For unknown cross intolerance, DP to a strong chemically unrelated non-selective COX inhibitor and towards the culprit NSAID if the former was negative.
- If still negative, evidence for cofactor enhanced food allergy was sought.

Results and Discussion

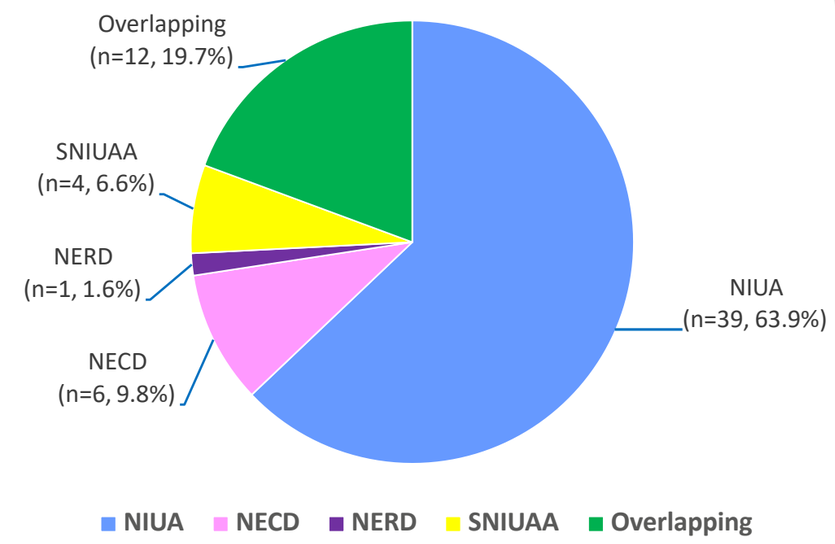

Figure 3. The frequency of the different phenotypes of NHS observed

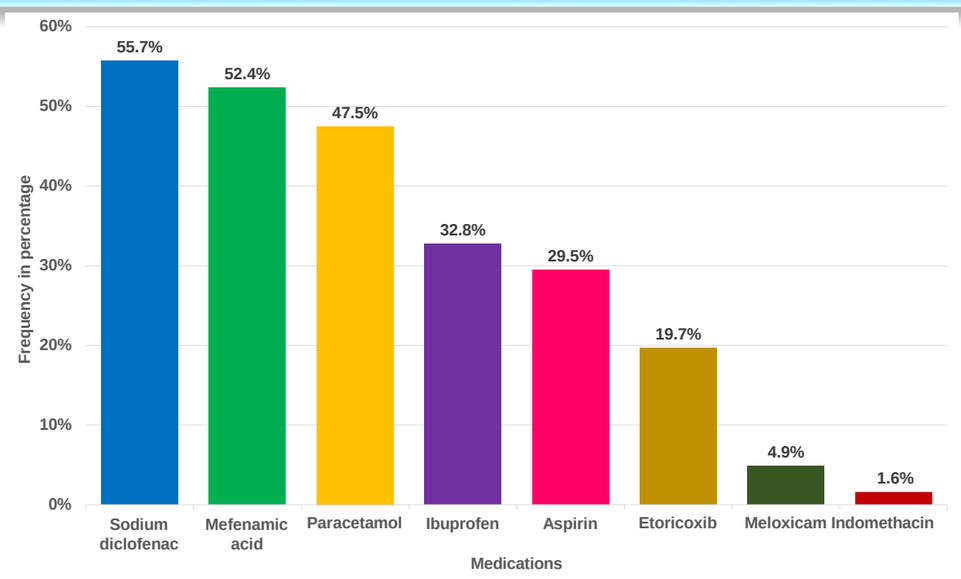

Figure 4. The percentages of the different triggering medications of NHS

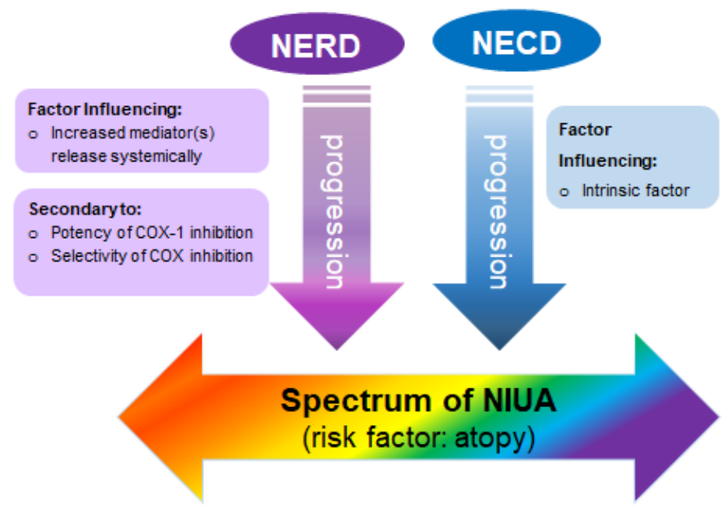

Figure 5. Hypothesis for the pathomechanism of the overlapping reactions.

- The mean age of the subjects during recruitment was 32.4 years (range 18-60 years). The male to female ratio was 1:3.
- Ninety-two percent of the subjects has one or more atopic diseases across all phenotypes. Allergic rhinitis (85%, n=53) with house dust mite sensitization (n=53) was the commonest underlying atopic disease.
- Four major phenotypes of NHS were observed namely NIUA (63.9%) followed by NECD (9.8%), SNIUAA (6.6%) and NERD (1.6%). However, 12 patients with chronic spontaneous urticaria, were diagnosed with overlapping symptoms (Figure 3).
- The five most common triggering NSAID was sodium diclofenac, (55.7%) followed by mefenamic acid (52.4%), paracetamol (47.5%), ibuprofen (32.8%) and aspirin (29.5%) (Figure 4).
- Interestingly, we observed that patients who developed reactions to low dose paracetamol (500 mg) will also react positively to COX-2 inhibitor(s) (n=9), however the reactions were mild (localized urticaria) and could be alleviated with antihistamines/leukotrienes inhibitors.
- For those who only reacted to high dose paracetamol (1000 mg), all were able to tolerate a low dose (45 mg) of etoricoxib (n=18).
- It was also observed that patients who developed reactions either to paracetamol or COX-2 inhibitor(s) would most likely develop reactions to tramadol as well (n=7).
- Based on the current observations, it strongly suggested that the CI NHS were dependent on the selectivity and potency of the COX-1 inhibition.
- Nevertheless, these observations warrant further confirmation by drug provocation on these specific drugs.
- These current findings suggest the hypothesis that the overlapping/blended reactions could be derived from a spectrum of a single NIUA entity (Figure 5) and future research is needed to elucidate this hypothesis.
- Additionally, three patients were diagnosed with NSAID-augmented wheat allergy and subsequently excluded from analysis of NSAIDs hypersensitivity (i.e. essentially an augmented food allergy reaction).
- This particular diagnosis was suspected when skin prick testing was positive to wheat and, specific IgEs to wheat and omega-5 gliadin, with suggestive history.
- These 3 patients were made to undergo a 5-step oral graded wheat provocation test with freshly prepared home-cooked high gluten flour fritter snack, with immediate exercise of 30 minutes following consumption.
- In addition to exercise, a total of 1.5 g of aspirin was added as co-factor (adapted & modified from Brockow et al, 2015). All three had positive responses

Conclusions

- **The current study demonstrates that NIUA is the commonest phenotype of NSAIDs hypersensitivity.**
- **Cofactor enhanced food allergy is an important differential to be considered when DP to the culprit NSAID was negative.**
- **It remains a challenging task to classify the overlapping symptoms which may be considered as a separate/converged phenotype for NSAIDs hypersensitivity.**

Acknowledgement

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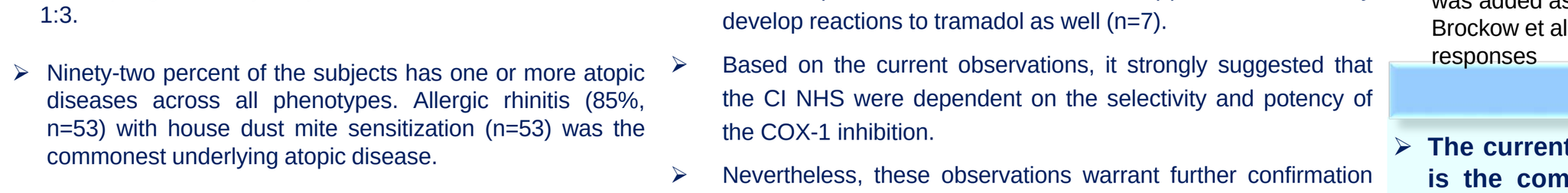

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