

CORRESPONDENCE

Classification of angioedema by endotypes

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We congratulate Powell et al.¹ for the development of the 'BSACI guideline for the management of chronic urticaria and angioedema', which is enlightening, and recognize the importance of NSAID as a trigger of angioedema. Recently, an international panel of HAE experts proposed a classification for 'angioedema without wheals'.² However, this classification did not include angioedema induced or exacerbated by NSAIDs, and the pathophysiological mechanisms of general angioedema were not completely addressed.² Although NSAID-induced or NSAID-exacerbated angioedema usually is associated with urticaria, it can also present as the sole manifestation of NSAID intolerance.

In our experience, NSAIDs are a major cause of drug-induced anaphylaxis³ and the major cause of angioedema without urticaria. We reviewed the records of 290 patients who sought medical assistance due to adverse drug reactions at the Adverse Drug Reaction Outpatient Facility of the 'Hospital das Clínicas', University of São Paulo School of Medicine, during 2013 and 2014. Patients who seek our hospital for chronic urticaria or aspirin-exacerbated respiratory disease were not included in the study. Forty-two percent of the patients ($n = 122$) had immediate hypersensitivity reactions (HSRs) to NSAIDs, with an average age of 40.8 years old, and 77.1% were female. Isolated cutaneous angioedema was observed in 27.9% (Fig. 1), and a 'familiar form' of HSRs to NSAIDs was observed in 11.5% of the cases. Patients presenting with simultaneous respiratory and cutaneous reactions, also called blended reactions, were counted as anaphylaxis cases.

Two major pathophysiological mechanisms of angioedema have been described: one induced by the activation of mast cells and/or basophils, resulting in release of histamine and other mediators (histaminergic angioedema), and other due to an excess of bradykinin (bradykinin-mediated or non-histaminergic angioedema), as seen in hereditary angioedema, acquired angioedema with C1-INH deficiency (lymphoproliferative and autoimmune disorders) and in angioedema induced by

angiotensin-converting enzyme inhibitors. HAE results from genetic mutations leading to C1-INH protein or function deficiency, or from the recently described mutations of factor XII.

Based on ours' and others' observations, we propose a classification of Angioedema based on endotypes (Fig. 2). Classifications based on endotypes provide insight into the aetiology and/or pathophysiological mechanism of diseases.^{4,5} The paradigm of personalized medicine is based on the principle that external stimuli (environment) induce diverse clinical manifestations (phenotypes), mediated by distinct pathophysiological processes (endotypes) in different individuals (genotypes).⁶

This angioedema classification based on endotypes (Fig. 2) includes the main causes of angioedema and is in agreement with the new information on the pathophysiology of the disease. Furthermore, it is consistent with angioedema consensus,^{1,2} and the 'hypersensitivity reactions to non-steroidal anti-inflammatory drugs' consensus.⁷ The high rate of patients with HSRs to NSAIDs with isolated angioedema emphasizes the importance of including this type of angioedema in the classification.

The understanding of angioedema subtypes and endotypes will allow the developing of new treatments for more effective disease management. Classification of angioedema by endotypes may identify patient groups that will benefit most from new and existing treatments

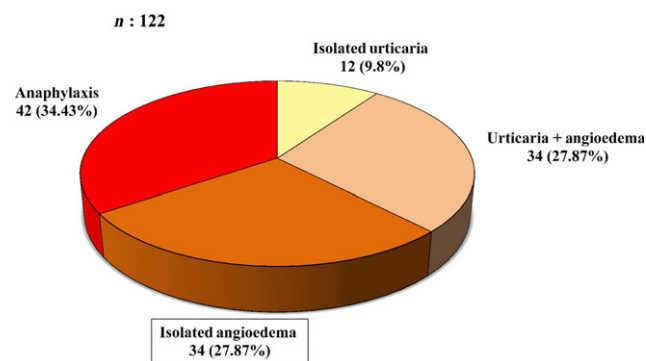


Fig. 1. Clinical manifestations of hypersensitivity reactions to non-steroidal anti-inflammatory drugs with cutaneous involvement.

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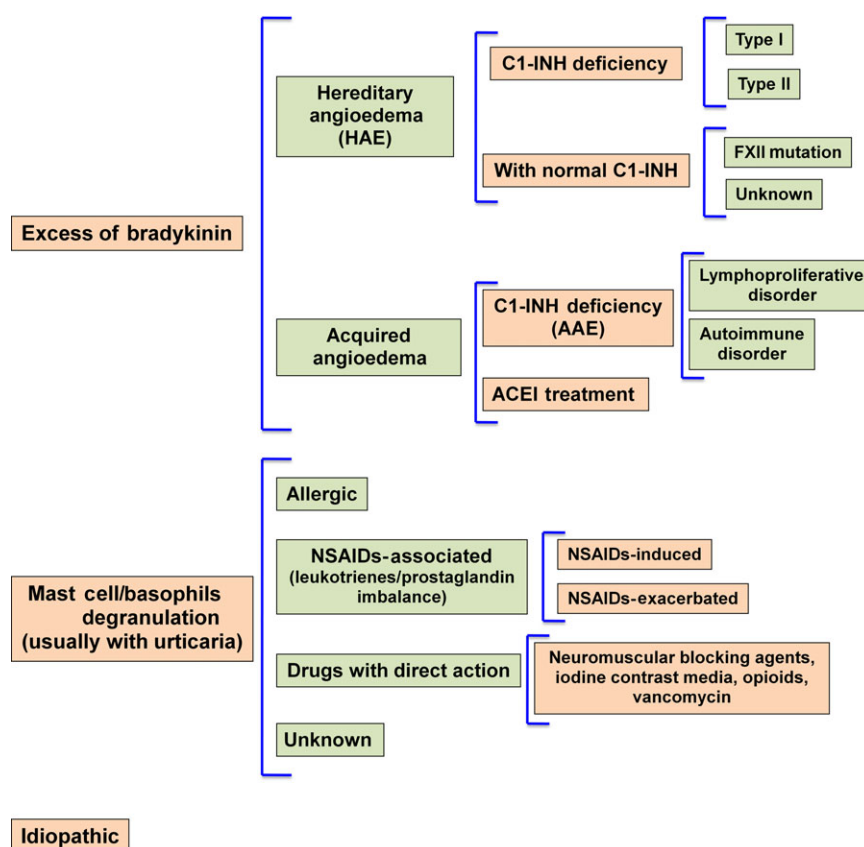


Fig. 2. Classification of angioedema by endotypes.

to substantially improve the patient-tailored care. The classification must also be dynamic and change as new knowledge is added to the field.

Conflict of interests

The authors declare no conflict of interest.

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