Differential Diagnosis and Management Issues of Idiopathic Angioedema and their Resolution

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ABSTRACT

Angioedema is a local and self-limiting swelling of the subcutaneous and sub mucosal tissues, produced by vasoactive peptides that temporarily increase the vascular permeability.

It is recognized that recurrent angioedema exposes patients to the risk of fatalities and reduced quality of life, being in some circumstances associated with a critical condition.

Angioedema can occur with or without wheals. The first symptom is urticaria, the second is a distinct nosologic entity. In absence of an identifiable cause, recurrent angioedema without wheals can be defined as idiopathic and marked “idiopathic histaminergic angioedema” when it is responsive to anti histamine treatment, and “idiopathic non-histaminergic angioedema” when it is not. Furthermore, idiopathic non-histaminergic angioedema can be diagnosed as hereditary or sporadic by family history.

In this review, we summarize the approaches to diagnose and treat different forms of idiopathic angioedema.

Keywords: angioedema, idiopathic, C1 inhibitor, factor XII, bradykinin, tranexamic acid

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INTRODUCTION

The word idiopathic derives from Greek ἴδιος (idios) "one’s own" and πάθος (pathos) "suffering". It is used by physicians when they cannot define the origin of a specific suffering any better than saying that it comes from itself.

In some cases, recurrent angioedema can expose patients to the risk of fatalities and therefore can be considered as a critical condition that requires prompt diagnosis and intervention.

In this paper, idiopathic angioedema refers to all forms of angioedema with unknown etiology and pathogenesis. Angioedema is a local, self-limiting oedema of the deep layers of the subcutaneous and submucosal tissues.

It occurs when inflammatory mediators bind specific receptors on the surface of endothelial cells. This binding activates the nitric oxide pathway and induces phosphorylation of the intracellular moiety of specific transmembrane proteins, collectively identified as tight and adherens junctions. These proteins occlude the gap between vascular endothelial cells and upon phosphorylation, pull apart adjoining cells, increasing vascular permeability [1]. Bradykinin, the best-characterized mediator of angioedema, is generally considered to exert its effect on vaso-permeability through this series of events [2].

Temporary cutaneous deformities, oral and upper airway oedemas and oedema of the gastrointestinal mucosa causing abdominal pain are the clinical equivalents of angioedema. The increase in vascular permeability and its attending symptoms, last from a few hours up to five days and vanish without persisting damage. Angioedema is symptom of urticaria when occurs with wheals, while angioedema without wheals is an independent nosologic entity encompassing different types. The first classification of recurrent angioedema without wheals [3] was published in 2014. This classification excludes allergic or para-allergic angioedema on the basis that they appear in close temporal relation.

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with exposure to specific factors and thus are not per se recurrent.

The 2014 classification distinguishes seven forms of recurrent angiooedema. Two are related to the deficiency of C1 inhibitor, either hereditary (C1-INH-HAE) or acquired (C1-INH-AAE). Less than ten years ago, mutations in factor XII (FXII) gene, segregating with the symptoms of angiooedema, were identified in families with angiooedema but lacking any C1-INH (FXII-HAE) deficiency. Another form of acquired angiooedema is related to treatment with the angiotensin converting enzyme inhibitors ACEI-AAE. Thus, four out of the seven different angiooedema have recognizable etiology, three “come from themselves” and can be defined as idiopathic [4-7].

Differential diagnosis of idiopathic angiooedema

Idiopathic angiooedema can be distinguished based on clinical presentation and on their response to therapy. Careful history taking can identify angiooedema symptoms within a family. The physician, when enquiring about angiooedema, should not limit his/her questions to cutaneous oedema, but should also include questions likely to disclose recurrent abdominal pain without identified origin, symptoms of laryngeal oedema and death in the family from sudden from acute respiratory distress, all of which can be presenting symptoms of angiooedema. On the other hand, symptoms of urticaria should not always be identified with a diagnosis of angiooedema. Distinguishing between angiooedema and wheals may not always be straightforward. Figure 1 details the facial symptoms in a patient with urticaria, and with C1-INH-HAE. These present as two distinct entities when directly compared, but can easily appear indistinguishable when patients try to give a description of these symptoms in relatives. In order to avoid an erroneous diagnosis of hereditary angioedema as opposed to urticaria, the concomitant presence of itching and erythematous wheals on the trunk and limbs should be looked for in the patient or reported in the history. Symptom location slightly changes in patients with different types of angiooedema and it has been reported in the literature that abdominal symptoms are detected more often in hereditary forms of angiooedema of unknown origin (U-HAE) than in patients with idiopathic non-histaminergic acquired angiooedema (InH-AAE) [8].

A major criterion in the differential diagnosis of idiopathic angiooedema is the response of the condition to therapy. It has been stated above, that angiooedema is due to the release of a vasodilating mediator. Clinical experience demonstrates that blocking H1-histamine receptors with specific antagonists such as H1-antihistamines, prevents the recurrence of angiooedema in some patients. Such angiooedema are defined as histaminergic, as it is assumed that histamines the primary mediator [9]. On the other hand, drugs that specifically block bradykinin B2 receptors effectively revert symptoms in

Figure 1. Panel A, angiooedema of the lips in a patient with chronic urticaria. Panel B, angiooedema of the lips in a patient with hereditary angiooedema due to C1 inhibitor deficiency. Note that in chronic urticaria the angiooedema tend to remain circumscribed while in the hereditary form it spreads to the surrounding tissues.
C1-INH-HAE, suggesting that this is a bradykininergic form of angioedema [10]. Although no controlled study has been conducted which evaluated the efficacy of H1-antihistamines in angioedema, these drugs are generally considered to be indicative of chronic urticaria. Extrapolating from this consensus, they are successfully used as a preventive measure in the treatment of chronically recurrent angioedema [11]. Response to H1-antihistamines given prophylactically can be used to identify patients with idiopathic histaminergic angioedema (IH-AAE). The highest dose of H1-antihistamine necessary to rule out IH-AAE is not univocally accepted. The standard recommendation [3,12] is to prescribe up to four times the recommended dose for chronic urticarial, though it has been shown that patients unresponsive to twice the registered dose, seldom if ever responded to further increases [13].

Figure 2 summarizes the position; when a patient has recurrent angioedema without wheals and appropriate workup excludes causative agents or conditions, angioedema is defined as idiopathic and accompanied by a relevant family history, it is diagnosed as HAE of unknown origin (U-HAE). In the absence of a relevant family history the idiopathic angioedema is classified as histaminergic (IH-AAE) or non histaminergic (InH-AAE) according to the response to H1-antihistamines. When histamine is excluded as a mediator consideration should be given to a diagnosis of bradykininergic angioedema, though it should be understood that only a few studies support bradykinin as a mediator of idiopathic angioedema [14] and subgroups with different pathogenesis should not be excluded. At present, the consensus is that only C1-INH-related and ACEI-related angioedema can be considered bradykinin mediated.

### MANAGEMENT OF IDIOPATHIC ANGIOEDEMA

Idiopathic angioedema that does not respond to H1-anti-histamine is frequently treated with drugs which have proved effective in the treatment of C1-INH-HAE. This drug can be used, either in the treatment of acute episodes, or as a prophylactic treatment. Most of the evidence to validating the response of idiopathic angioedema to therapies is reported in case reports and
It is recognized that recurrent angioedema exposes patients to the risk of fatalities and reduced quality of life. C1-INH-HAE has been assessed in terms of number of recurrences, number of disease related deaths and economic impact [15-20]. Similar reports for idiopathic angioedema are not available, nevertheless it is known that the symptoms are analogous and deaths can occur [9,21,23]. Hence, there is need for effective treatment aimed at reducing morbidity and avoiding mortality. The estimated mortality of C1-INH-HAE, in absence of specific diagnosis and treatment, is about 25%. Nevertheless, specific drugs are available for the treatment of life-threatening attacks to patients with C1-INH-HAE. The same cannot be done for idiopathic angioedema. The first line approach for any patient with angioedema is corticosteroids, anti H1 histamine and epinephrine in the presence of laryngeal involvement [24]. This approach is suitable for conditions originating from mast-cell activation and it is indeed justified since angioedema of this origin is certainly the most common. However, general experience indicates this approach to be scarcely effective in non-histaminergic idiopathic angioedema. Solid data confirming this statement are absent and evidence of inefficacy are grounded in a patient’s retrospective history. We have adopted the policy to continue recommending with our patients, corticosteroids, anti H1 histamine and epinephrine (if necessary) as first choice for acute treatment. When this approach is confirmed to be ineffective, bradykinin targeted drugs are considered, this approach being based on several studies [25-33]. These drugs have been indicated for C1-INH-HAE and include plasma derived and recombinant C1-INH, a recombinant inhibitor of plasma kallikrein and the antagonist of bradykinin receptors [10,24-37]. Fresh frozen plasma, used to replace C1-INH when specific concentrates are not available, can also be an option to replace an unidentified deficiency leading to bradykinin release.

Controlled studies which provided the evidence that is needed to appropriately treat these differing entities, starting with an initial effort of classifying angioedema within specific groups [3] is called for.

The same problem also applies to prophylactic treatment of the disease. This approach, aimed at administering treatment in absence of signs of angioedema in order to prevent its occurrence, may result in a continuous lifelong therapy. Embarking on such a course of treatment requires careful risk benefit evaluation, weighting efficacy and side effects and consideration of the impact on the quality of life. None of these assessment relays on specific tools and the decision relies on the physicians’ clinical judgment and the patients’ informed evaluation. As a general recommendation, prophylaxis is considered when patients experience two or more attacks per month that impact on their daily activities. Choosing the drug in the absence of a recognized aetiology should be made after first undertaking an epidemiologic evaluation. Idiopathic angioedema mediated by histamine appear to be more common and it is therefore recommended to start with a second-generation H1-antihistamines such as azelastine, bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine or mizolastine. A dose, double that recommended for allergic diseases, increasing to three times in presence of a partial response, has been recommended. There are no rules for dose tapering in responsive patients, and the view has been expressed in the literature, that it is better not to consider any reduction before three months of successful treatment. When anti H1-histamine fails, tranexamic acids should be considered as the first choice for prophylaxis of these non-histaminergic idiopathic angioedema [9,25,32,38]. Efficacy of this drug seems to cover also hereditary forms with unknown pathogenesis [22]. Doses up to three grams per day can be used, tapering to the effective dose according to the achieved clinical response. Thrombotic risk should be assessed before prescribing this treatment, due to its clot stabilizing activity [39].

Little experience has been reported in the literature on the efficacy of the anti-IgE omalizumab in idiopathic angioedema [40]. This, as with other treatment used in histamine resistant chronic urticarial, has been considered for non-histaminergic angioedema, but no reported recommendation for their use appear in the literature.

**Conclusions**

Recurrent angioedema is a condition that can expose patients to a critical clinical condition or even death. The prompt diagnosis and intervention is therefore crucial in these cases, in order to prevent the development of serious complications. In absence of specific
diagnosis and treatment, the estimated mortality of C1-INH-HAE, is as high as 25%, underlining the need for a correct treatment of the life-threatening attacks to patients with C1-INH-HAE. Furthermore, prophylaxis regimens should be considered whenever the patients experience two or more attacks per month, and should be adapted to the specific form of angioedema.

The studies on the mechanisms of \textit{in vivo} activation of the contact system are expected to clarify the pathogenesis of hereditary angioedema associated with FXII mutations and possibly the mechanisms involved in some idiopathic angioedema. This research should end up in target for diagnosing, monitoring and treating these patients, having a great potential to be translated into a better life for patients.

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\section*{Conflict of interest}

None

\section*{References}


