The Clinical Evaluation of Angioedema

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KEYWORDS

• Angioedema • Bradykinin • Histamine • Hereditary angioedema

KEY POINTS

- Angioedema may occur through several mechanistic pathways. An understanding of the pathophysiology aids in the evaluation, clinical diagnosis, and management of this condition.
- Angioedema can be broadly categorized into episodes occurring with or without urticaria; after this distinction is made, this allows for the further differentiation of angioedema subtypes.
- The initial step in the clinical evaluation of angioedema is obtaining a thorough patient and family history, while giving consideration to differential diagnoses and angioedema mimickers.
- Although episodes of angioedema without urticaria may be clinically similar in presentation, there are characteristics and laboratory parameters that are unique to each subtype. Applying an algorithmic approach based on these parameters allows one to reach an accurate diagnosis.
- Further research in the clinical evaluation of angioedema directed at developing a greater understanding of the pathophysiology should enable the development of new diagnostic assays and novel targeted treatments.

INTRODUCTION

Angioedema, also known as Quincke edema or "angioneurotic edema," was first described by Marcello Donati in 1586 in reference to a young count who developed lip swelling as a result of an egg allergy.[1] The first reference to hereditary angioedema resulting in fatal suffocation was reported by Osler in 1885.[2]

It is estimated that up to 25% of the US population will experience an episode of urticaria with or without angioedema during their lifetime.[3] Angioedema is defined

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as the localized nonpitting edema of deep dermal, subcutaneous, or submucosal tissues resulting from the increase in vascular permeability and extravasation of intravascular fluids; although it can coincide with urticaria in a histamine-mediated process, a differentiating feature is that urticarial wheals are limited to the mid and papillary dermis.[3]

This article serves as a general overview of the clinical evaluation of angioedema with and without urticaria and focuses on the following:

1. Signs and symptoms of angioedema
2. Classification of angioedema subtypes
3. Pathophysiology
4. An approach to the clinical evaluation of angioedema
5. Diagnostic evaluation in angioedema
6. Future directions in the evaluation of angioedema

More detailed discussion about angioedema mechanisms and treatments will be presented in other sections of this issue of *Immunology and Allergy Clinics of North America*.

SIGNS AND SYMPTOMS OF ANGIOEDEMA

The presentation of angioedema may vary between subtypes, although in all forms, it can occur at any site of the body and some organ tissues. The edema itself is nonpitting, typically with ill-defined borders, and may be flesh-colored or erythematous in nature. Episodes of swelling may be accompanied by pruritus and urticaria, in the case of histamine-mediated forms, or associated with a burning and tingling sensation.

The most commonly involved sites include the following:

1. Head and neck: Angioedema affecting the eyelids, lips, tongue, and larynx, with the possibility of life-threatening airway obstruction
2. Peripheries: Swelling of the hands, feet, and urogenital areas
3. Abdomen: Angioedema may mimic symptoms of an acute abdomen, resulting in surgical intervention

Examples of these site-specific swellings are depicted in **Fig. 1** and **Fig. 2**.

Several factors are known to increase the probability as well as the severity of specific angioedema subtypes as discussed later, but can include foods and medications resulting in direct mast cell degranulation (ie alcohol, non-steroidal anti-inflammatory drugs [NSAIDs]), stress, dental or surgical manipulation, and hormonal factors.[4,5]

PATHOPHYSIOLOGY OF ANGIOEDEMA

Acute episodes of angioedema result from a release of vasoactive mediators that increase vascular permeability in the skin and submucosa, allowing for the vascular leakage of plasma and resultant edema; most of these attacks can be attributable to the following.

Histamine-Mediated Pathways

Immunoglobulin E (IgE)-mediated reaction begins with a primary response and typically occurs within seconds to minutes of exposure to an allergen, from the release of vasoactive amines such as histamine, and results in increased vascular permeability, smooth muscle contraction, vasodilation, glandular secretions, and bronchospasm.[6]