

Isolated angioedema: An overview of clinical features and etiology (Review)

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Abstract. Angioedema can occur in isolation, accompanied by urticaria, or as a feature of anaphylaxis in mast cell-mediated disorders, bradykinin-mediated disorders, as well as in others with unknown mechanisms, such as infections, rare disorders, or idiopathic angioedema. In mast cell-mediated angioedema, other signs and symptoms of mast cell-mediator release are frequently seen. However, clear evidence of mast cell degranulation may be absent in histaminergic angioedema. Bradykinin-induced angioedema is not associated with urticaria or other symptoms of type I hypersensitivity reactions. For many of the known triggers of angioedema, the mechanism is unclear. While mast cell and bradykinin-mediated angioedema are relatively well defined in terms of diagnostic and therapeutic approach, angioedema with unknown mechanisms represents a challenge for patients and clinicians alike. Elucidating the clinical pattern and the possible causes of isolated angioedema is the key to a correct diagnosis. This review summarizes the causes, and clinical features of angioedema, with a focus on isolated angioedema.

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1. Introduction

From a historical perspective, Quincke, a German internist and surgeon first described angioedema, in 1882 (1). Six years later, Osler recognised the hereditary nature of the disease (2). Angioedema manifests as localized, asymmetric, typically nonpruritic cutaneous and/or mucosal swelling, predominantly affecting areas with loose connective tissue. Certain clinical features differentiate angioedema from other types of edema (Table I) (3,4). Angioedema can occur in isolation, accompanied by urticaria, or as a feature of anaphylaxis in mast cell-mediated disorders, bradykinin-mediated disorders, as well as in other conditions with unknown mechanisms, such as infections, rare disorders, or idiopathic angioedema. In mast cell-mediated angioedema, other signs and symptoms of mast cell-mediator release (flushing, urticaria, pruritus, and other end-organ manifestations, such as rhinorrhea, nasal obstruction, bronchospasm, wheezing, dysphonia, stridor, dysphagia, diarrhea, abdominal pains, nausea, vomiting and cardiovascular symptoms) are frequently seen. In contrast, bradykinin-induced angioedema is not associated with urticaria or other symptoms of type I hypersensitivity reactions. Clinical response to antihistamines is a cardinal feature of mast cell-mediated angioedema, also known as histaminergic angioedema, while bradykinin-mediated angioedema is non-histaminergic, or refractory to antihistamine therapy (3).

In this review, the possible causes and the clinical picture of angioedema, with a focus on isolated angioedema are discussed.

2. Clinical forms of angioedema

Two main clinical forms of angioedema have been described: mast cell-mediated angioedema and bradykinin-mediated angioedema (Table II) (3,5).

Mast cell-mediated angioedema generally is accompanied by signs and symptoms of mast cell-mediator release, such as urticaria and not only; it onsets within minutes to hours after allergen exposure, resolves in 24-48 h, and usually responds to antihistamine treatment (4).

Bradykinin-mediated angioedema encompasses a spectrum of rare disorders in which the angioedema is isolated, thus not associated with urticaria, or with other signs of

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Table I. Clinical characteristics of angioedema versus other forms of edema.

Angioedema	Other types of edema
Self-limited, with asymmetric distribution	Chronic, persistent, symmetric
Onsets in min/h	
Spontaneous resolution in hours/several days	
Non-gravitational, non-position dependent	Tendency to involve gravitational dependent areas; symptoms and signs are related to position
Involves areas with loose connective tissue (lips, eyelids, mouth, throat, uvula, larynx, extremities, genitalia, bowel wall)	Affects other areas, depending on the underlying condition
Associated with other signs of allergy or anaphylaxis ^a	Lack of signs of allergy/anaphylaxis

^aIn cases of histaminergic angioedema.

allergic reactions. It usually builds within hours or days, the relationship between the trigger and the inaugural symptoms is not apparent, and it resolves within two to four days. In addition, it does not respond to antihistamine therapy, regardless of dose. In addition, it does not respond to corticosteroids, while epinephrine brings a mild and transient clinical benefit.

Hereditary angioedema (HAE) or inherited C1 inhibitor (C1INH) deficiency is a rare genetic disease caused by deficiency (type I) or dysfunction (type II) of C1INH. Mutations of the C1INH gene, SERPING1, are the main abnormality in both HAE subtypes (6,7).

HAE due to C1INH deficiency is an autosomal dominant disorder with an almost complete penetrance affecting 50% of male and female children of parents with HAE. The overall prevalence ranges from 1:30,000 to 1:80,000 in the general population. Type I HAE accounts for approximately 85% of cases, with type II HAE affecting the other 15% (8).

In addition, a type III form of HAE, with C1INH normal function and expression has been described. No mutations of the SERPING gene were identified in affected individuals. Type III HAE also shows an autosomal dominant pattern of inheritance. It predominantly affects female population and it tends to be less severe in the minority of men suffering from the disease. Mutations in the factor XII gene were identified in some of the cases. In addition, estrogens exacerbate the disease in many of the affected individuals (9).

All clinical forms of HAE are characterized by recurrent attacks of isolated nonpruritic, nonpitting angioedema, affecting the extremities, genitourinary, upper respiratory and gastrointestinal tracts (10). There is a wide variability in the kinetics of angioedema episodes. Usually, angioedema develops gradually, builds in the first 24 h, is self-limited, but temporarily debilitating, usually resolving over the next 48-72 h. However, some attacks progress rapidly, within minutes, while others last for more than 5 days. Fatalities from laryngeal attacks have been reported. Angioedema episodes most commonly involve the extremities and the gastrointestinal tract, with each accounting for approximately 50% of all attacks. More than half of the patients will experience at least one laryngeal attack (11). Infrequently, angioedema has a different distribution, involving the brain, heart, kidney, or joints. Prodromal symptoms, such as erythema marginatum,

a sense of skin tightening or localized tingling, as well as nonspecific manifestations (fatigue, malaise, flulike symptoms, thirst, nausea, and mood changes) precede the attacks by 24-48 h in up to 50% of patients (8,10). Concerning the onset of the disease, the clinical picture becomes clinically apparent before the first ten years of life in almost 50% of cases, with some cases manifesting the disease by the first year of age. The disease tends to worsen during puberty and to improve with aging. However, some patients continue to experience attacks throughout their life. Rare cases of HAE patients who do not exhibit the disease were identified. HAE exacerbations are episodic, with some patients experiencing symptoms as frequent as twice a week. The pattern of disease severity is variable and individual (8,10,12,13). The disease significantly impairs the quality of life. Genitourinary attacks may lead to temporary anuria, while gastrointestinal tract attacks can result in severe symptoms and the formation of 'third spacing' of fluid can induce hypotension (8).

Several precipitating factors have been identified: mild trauma and iatrogenic trauma, such as dental surgery, intubation, or other medical procedures, emotional stress, pregnancy, and estrogen therapy. In addition, ACEI therapy has the potential to unmask an underlying HAE. Trauma and emotional stress proved to be the most frequent triggers of symptoms. The level of trauma required to induce symptoms varies greatly from one patient to another. In some cases, mild trauma, such as clapping of hands or prolonged sitting may cause an attack (8,14).

Acquired C1INH deficiency is sporadic and relatively rare, accounting for 1:100,000 to 1:500,000. Both sexes are equally affected and it preponderantly occurs in the elderly, particularly in those with autoimmune or lymphoproliferative disorders. The proposed mechanism is the presence of autoantibodies against C1INH. A 2016 study reported that 33% of patients presenting with acquired angioedema had or would develop non-Hodgkin lymphoma. The enrolled patients (62.5%) were diagnosed with non-Hodgkin lymphoma at the onset of angioedema or up to 7 years later (15). Acquired angioedema has been associated with several other disorders (Table III).

Angiotensin convertase inhibitor induced angioedema represents up to 40% of angioedema cases referred to the Department of Emergency (36). Angioedema occurs in 0.1-0.7% of patients treated with ACEI. Of these, 25-39%

Table II. Types of angioedema.

Type	Pathophysiology	Affected population	Prevalence
Bradykinin-mediated angioedema (non-histaminergic)			
Type I HAE	C1INH deficiency, caused by mutation in SERPING1 gene	All	~1:50,000
Type II HAE	Functional C1INH deficiency, caused by SERPING2 gene mutation	All	~1:250,000
Type III HAE with normal C1INH (both antigen and function)	Unknown, some of the patients exhibit defects in factor XII gene	Predominantly women	Unknown
Acquired C1INH deficiency	Deficiency of C1INH by consumption, or blocking by autoantibodies against C1INH	Older patients, frequently linked to underlying disease (autoimmune, lymphoproliferative disorder)	~1:250,000
ACEI-induced angioedema	Inhibition of bradykinin catabolism	All, with an increased prevalence in African-Americans	~1:250
Non-histaminergic idiopathic	Unknown	Unknown	Unknown
Mast cell-mediated angioedema (histaminergic)			
Angioedema accompanied by acute urticaria	Release of histamine	All	~20% of population
Angioedema in the context of anaphylaxis	Release of histamine	All	0.3-5.1% of population
Angioedema accompanied by CU	Release of histamine	All, more common in adults, women affected twice as often as men	CU affects ~1% of population 40% of cases associate angioedema. Angioedema is the main manifestation in 10% of CU cases

HAE, hereditary angioedema; C1INH, C1 esterase inhibitor; SERPING, serpin family G member; ACEI, angiotensin-converting-enzyme inhibitor; CU, chronic urticaria.

affects the upper respiratory tract, being potentially lethal. Most often, angioedema is located at the cephalic extremity, manifesting as palpebral, lingual or lips edema, or even laryngeal edema, which, in severe forms, can lead to death by asphyxia, but can also affect the digestive tract: abdominal pain syndrome, nausea, vomiting, with sudden onset. Sartans may induce similar ACEI manifestations. Patients with ACEI-induced angioedema (1.5-10%) develop angioedema to sartans. Administration of ACEI or sartans may unmask an underlying hereditary angioedema. In this context, it is recommended to rule out HAE in cases of ACEI/sartan-induced angioedema (3). Approximately 50% of cases occur as early as in the first week of treatment (16,17). Sometimes, angioedema or digestive manifestations may occur years after initiation of ACEI/sartan therapy (8). Angioedema is intermittent despite the daily therapy, which may cause confusion and misdiagnosis. Moreover, attacks can reoccur weeks or months after treatment discontinuation (18). Overproduction and/ or reduction of bradykinin degradation induces vasodilation and increased vascular permeability, clinically expressed by isolated angioedema and is the mechanism of production of this disease. Mast cells do not degranulate, which is why

pruritus and urticaria are absent. The mechanism by which sartans induce angioedema is insufficiently elucidated (3,8).

3. Conditions that mimic angioedema

Several disorders may be mistaken for angioedema. Cutaneous edema is found in contact dermatitis, cellulitis, erysipelas, rosacea, autoimmune disorders, superior vena cava syndrome, parasitic infections, hypothyroidism or cheilitis granulomatosa.

Contact dermatitis can cause dramatic facial and/or eyelid swelling in response to topical agents (cosmetics or pharmaceutical). Clinical signs, such as erythema, pruritus, or burning of the skin are indicative of contact dermatitis and help rule out the diagnosis of angioedema. In addition, resolution of contact dermatitis may cause peeling, which is absent in angioedema (37).

In contrast to angioedema, cellulitis and erysipelas are accompanied by erythema, pain, and may be associated with fever. Rosacea may be associated with facial lymphedema. However, flushing and warmth of the face, which are typical features of rosacea, are absent in angioedema.

Table III. Conditions associated with angioedema.

Conditions	Refs.
Hypereosinophilic syndrome	(19)
Gleich syndrome	(20)
T-cells lymphoma	(21)
Multiple myeloma	(22)
Chronic lymphocytic leukemia	(23)
Myelofibrosis	(24)
Waldenström macroglobulinemia	(25)
Non-Hodgkin lymphoma	(15)
Essential cryoglobulinemia	(26)
Cold urticaria	(27)
Urticaria vasculitis	(28)
Livedo reticularis	(29)
Lupus, scleroderma	(30,31)
Rectal carcinoma	(32)
MGUS	(33)
Infection with <i>Helicobacter pylori</i> or <i>Echinococcus granulosus</i>	(34,35)

MGUS, monoclonal gammopathy of uncertain significance.

Blepharochalasis syndrome, characterized by recurrent episodes of upper eyelid unilateral or bilateral edema, leading to atrophy and discoloration of the affected skin may be mistaken for angioedema (38). Facial edema can be seen in patients with autoimmune disorders, such as lupus and in early stages of scleroderma (31). Hypothyroidism causes, in severe forms, myxedema, persistent generalized edema or edema of the face. Parasitic infestations with American trypanosomiasis (Chagas disease) can cause significant palpebral and periorbital edema, also known as Romana's sign (39).

Superior cava syndrome, and head and neck, lymphoma, or pulmonary tumors can induce persistent, progressive, localized edema (40). Melkersson-Rosenthal syndrome or Miescher's cheilitis (cheilitis granulomatosa) is a rare disease, consisting of initially recurrent and eventually permanent facial and lip angioedema, which may be mistaken for angioedema. Geographic tongue and neurological findings in these patients help to confirm the diagnosis (41). Generalized recurrent edema can also occur in some female patients during their menstruation. Sometimes, it is impossible to place angioedema in a clinical context. In clinical practice, idiopathic nonhistaminergic angioedema cases are increasingly seen.

4. Conclusions

Angioedema typically manifests as bouts of swelling involving cutaneous or mucosal surfaces. Most often, angioedema is mast cell mediated, being included within the spectrum of urticarial disorders. However, non-mast cell-mediated forms of angioedema can pose difficult challenges to clinicians. Isolated non-histaminergic angioedema is found in types I-III hereditary angioedema, in several acquired forms of angioedema, associated to ACEI/sartan therapy, or with a myriad of hema-

tological, autoimmune, or neoplastic disorders. ACEI/sartan induced angioedema may unmask an underlying hereditary angioedema. Elucidating the clinical features and the possible causes of isolated angioedema is the key to a correct diagnosis.

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Competing interests

The authors declare that they have no competing interests.

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