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Recurrent angioedema: diagnosis strategy and biological aspects

The aetiologies of recurrent angioedema (AE) comprise the frequent histaminergic AE and the rare bradykinin-mediated AE. Diagnosis must be done carefully because they do not have the same treatment. Diagnosis strategy is clinical. The most specific symptoms for bradykinin AE are: isolated AE without wheals, long duration of the attack, abdominal localisation. The unique useful biological tests for the diagnosis of bradykinin AE are C1Inh exploration which is altered in hereditary AE (HAE) types I and II. No other biological test is useful in clinical practice at present. In case of suspicion of bradykinin AE with normal C1Inh, physicians must think of drug-induced AE. Hereditary AE with normal C1Inh may be associated with a mutation on gene F12 in 20% of cases. For 80% of patients without mutation, the diagnosis must be done very carefully.

Key words: angioedema, urticaria, histamine, bradykinin, C1Inh, diagnosis

Angioedema (AE) is a clinical symptom characterised by sudden localised swelling of subcutaneous and/or submucous tissues (*figure 1*). This is a hypodermic oedema [1]. The swelling is skin-coloured,



Figure 1. Angioedema of the face.

sometimes pink but never red. Pruritus is absent or slight. It is not inflammatory and not permanent. It disappears without sequelae and may recur. Its annual incidence in the general population is estimated at 0.05% [2]. The principal causes of recurrent angioedema are histaminic with IgE (allergic) or non-IgE mastocyte-mediated activation, the latter being linked to chronic urticaria [3] (*figure 2*).

A much rarer form is inherited, acquired or drug-induced bradykinin-mediated angioedema (*figure 3*) [4]. The diagnosis of bradykinin AE must not be missed, since these forms are resistant to treatments of histamine AE (adrenalin and antihistamines). They respond to a specific efficacious treatment, but this has cost implications. Bradykinins AE are classified according to whether they are associated with C1Inh deficiency (inherited type I and II or acquired) or

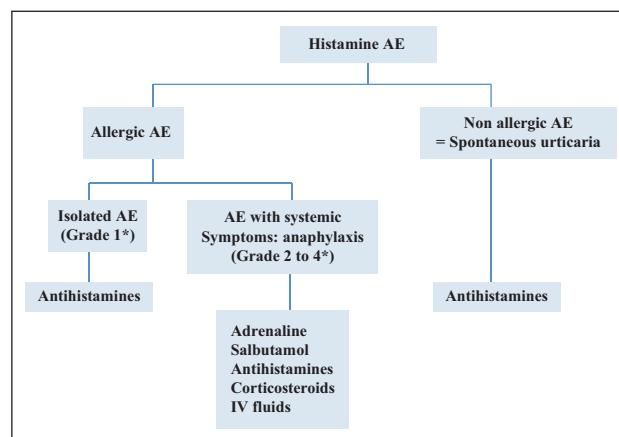


Figure 2. Diagnostics and treatment of Histaminergic AE.
 * Classification of Ring and Messmer [20, 21].

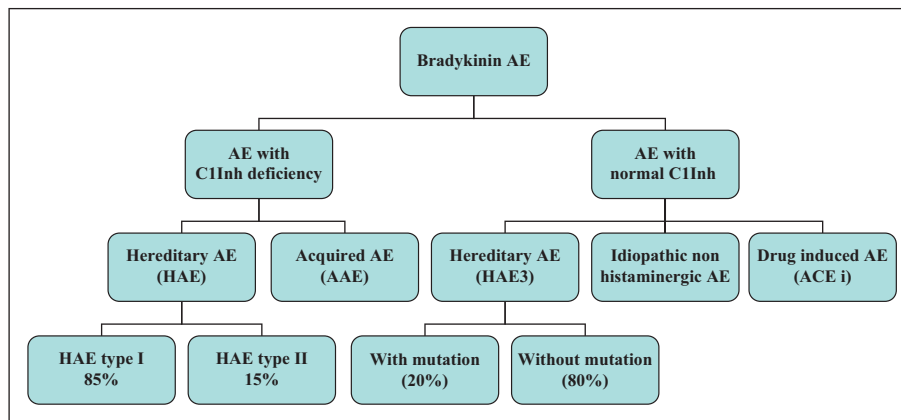


Figure 3. Bradykinin-mediated AE classification.
ACEi: angiotensin converting enzyme inhibitors.

with normal C1Inh (HAE3 or iatrogenic AE secondary to treatment with angiotensin conversion enzyme inhibitors (IECi) [5].

Diagnostic strategy (table 1)

Distinguishing between bradykinin AE and histaminergic AE is at present mainly based on clinical considerations [6]. If the AE is isolated (without visceral signs) and mainly affects the face, the lips and the eyelids, the differential diagnosis between bradykinin and histaminergic AE is the most difficult. The higher frequency of histamine relative to bradykinin AE leads us to consider this one in the first instance.

Histaminergic AE is often associated with chronic urticaria [2] with episodes of wheals, concomitant or not with AE (figure 4). This is far from being an obligatory condition, however, since isolated AE without associated urticaria represent 10% of cases, it is probably an under-estimate. Bradykinin AE are not associated with wheals. They are sometimes preceded by a reticulated rash called erythema marginatum (figure 5), which should not be confused with an urticarial rash [7]. This means that an angioedema with no associated urticaria is not necessarily bradykinin-mediated. The second factor which can exclude bradykinin AE is the duration. Bradykinin AE persists for at least 24 hours, rarely for less. Histamine AE, however, may persist for more than 24 hours (e.g. NSAID-induced), particularly

if systemic corticosteroids were used in treating previous attacks, inducing a corticosteroid-dependent status [8]. A diagnosis of histamine-mediated angioedema is based on the response to antihistamine treatment. The therapeutic strategy in histamine AE is thus the same as in chronic urticaria, where we propose increasing doses of antihistamines (up to 4 times the usual daily dose) [9]. An AE is considered to be histamine-resistant if the frequency and severity of attacks are not changed by taking 4 times the usual daily dose of antihistamines. An antihistamine-resistant AE is not, however, synonymous with bradykinin AE. In this setting, antihistamine resistant AE may be induced by the long term use of a corticosteroid [8].

Bradykinin AE may be localised in the abdominal region and may cause recurrent sub-occlusive scenarios with spontaneous recovery after 48-72 hours [7]. They are accompanied by severe pain (visual analog pain scale >7 in 69% of cases), sometimes by blood pressure disorders, nausea and vomiting, often with severe diarrhoea at the end of the attack. Medical imaging (scan or ultrasound) reveals ascites and/or oedema of the walls of the digestive tract. Association of facial AE with peripheral oedemas and abdominal crises is highly specific to bradykinin AE (10). The existence of a family context supports bradykinin AE, although it is important to note that i) 25% of angioedemas associated with C1Inh deficiency are secondary to a *de novo* mutation (therefore no family context in ancestors) [7]; ii) histamine AE that often occurs as isolated facial AE may have also a familial context [7].

Table 1. Clinical data for recurrent AE diagnosis.

	Bradykinin AE	Histaminergic AE
Wheals	No	Yes but not always
Duration of attack	Some days (usually >24 h)	Some hours (>24 h possible)
Abdominal attack	Frequent	Rare
Context	Family, drugs (ACEi, estrogens)	Atopy, drugs (NSAID. . .)
Long term prophylaxis with anti histamine	Inefficient	Efficient

ACEi: angiotensin converting enzyme inhibitors; NSAID: non steroid anti inflammatory drugs.



Figure 4. Urticaria.



Figure 5. Erythema marginatum before HAE attack.

The most frequent bradykinin AE are those associated with taking ACE inhibitors, which account for 17 to 34% of AE presenting as emergencies [11]. They should be considered in any patient taking an ACE inhibitor either under treatment or having taken an ACE inhibitor in the year prior to the AE. A recent study shows that, even though ACE inhibitors have been withdrawn, angioedemas may recur 6 or even 12 months thereafter [12].

Biological diagnosis (*table 2*)

Apart from C1Inh investigation, there is at present no reliable biological test to distinguish between bradykinin and histamine AE.

- 1. Diagnosis of histamine AE: Histamine has a short half-life (a few minutes), which limits the usefulness of its measurement to support a diagnosis. Histaminuria is not sufficiently specific. As in chronic urticaria, biological analysis should be limited in recurrent histamine-mediated angioedema [14].
- 2. Diagnosis of bradykinin AE without C1Inh deficiency (Type III AE, ACE inhibitor AE) is not possible at the present time. The very short half-life of bradykinin (a few minutes) prevents its reliable and repeatable measurement [15]. Bradykinin AE with normal C1Inh (HAE3) have no specific biological marker at present. Diagnosis is exclusively clinical. To finalise a diagnosis of AE with normal C1Inh, one can search for a mutation of gene F12, present in 15-20% of patients [16].
- 3. Diagnosis of bradykinin AE associated with C1Inh deficiency (hereditary: Type I and II HAE, or AAE): quantitative and functional investigation of C1Inh and measurement of C4 allow a diagnosis to be reached [17]. A reduced level of C1Inh must be confirmed in two separate samples. Levels should be considered pathological if antigenic concentrations of C1 inhibitor are below 50% of normal values. Functional levels of C1 inhibitor are considered abnormal if the level is below 50% (chromogenic assay) or 84% (ELISA assay; local normal ranges might vary) of normal values (*table 3*) [18]. A simultaneous low level of C4 supports the pathological character of the low C1Inh level. Prudence must be exercised when interpreting a small reduction in the level of C1Inh. The functional level of C1Inh is physiologically lowered during pregnancy and when combined pills are being taken without pathology [19, 20]. In these physiological contexts, the level of C4 is normal. C1Inh measurements should be interpreted with caution. In the context of pregnancy, assays must be repeated a few weeks after delivery.

If HAE is suspected because of C1Inh deficiency, searching for a mutation of the SERPING1 gene should not be systematic, since a measurement of C1Inh and family questioning are sufficient for a diagnosis of HAE type I/II. In certain very rare cases, there may be diagnostic doubt between a hereditary or acquired form. Acquired forms due to C1Inh

Table 2. Exploration in recurrent AE

Histaminergic AE
None if isolated
Tryptase if associated with signs of anaphylaxis.
Bradykinin AE:
C1Inh antigenemy and function
C4
+/- C1q and anti C1Inh antibody
+/- Mutation <i>SERPIN G1</i>
+/- Mutation <i>F12</i>

Table 3. C1Inh exploration and Bradykinin AE classification. AAE: Acquired angioedema; HAE: hereditary angioedema; ACEi: angiotensin converting enzyme inhibitor.

AE	C1Inh deficiency			Normal C1Inh	
	HAE type I	HAE type II	AAE	HAE3	ACEi AE
C1Inh antigenemy	<50%	Normal	<50%	Normal	Normal
C1Inh function	<50% (Chromogenic) <85% (ELISA)	<50% (Chromogenic) <85% (ELISA)	<50% (Chromogenic) <85% (ELISA)	Normal	Normal
C4	Low	Low	Low	Normal	Normal
C1q	Normal	Normal	Low (70%)	Normal	Normal
anti C1Inh antibody	No	No	Yes (50%)	No	No
Mutation	SERPING1 (90%)	SERPING1 (90%)	None	F12 (15%)	None

deficiency often have a low C1q level (80% of cases). AAE may be linked to anti-C1Inh antibodies. A dysglobulinemia of indeterminate origin is often present at the same time [21].

Conclusions

The etiological diagnosis of recurrent AE is a clinical exercise. If bradykinin AE is suspected, advice should be sought from experts of angioedema. A diagnosis of bradykinin AE must not be missed but neither should one fall into the trap of over-diagnosis. A wrong diagnosis may have dramatic human consequences and serious financial implications. ■

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