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Review Article

Angioedema: General Overview

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Abstract

Angioedema diagnosis is usually evident at clinical level. However a precise etiological diagnosis can be more difficult because clinical manifestations are lack of specificity and there are multiple possible causes. A precise diagnosis will not be achieved if the clinician does not have a clear overall view of angioedema. In the present article we try to offer an overview of main features of more important causes of angioedema in order to aid clinicians in their practical activity.

Introduction and Pathophysiological Notes

AE is a rare condition. Hereditary Angioedema (HAE) has an estimated prevalence of 1 in 50.000 to 100.000 of the population [1,2]; the prevalence of Acquired Angioedema (AAE) due to C1-Inh deficiency is unknown, but it has been estimated in 1 for every 10 patients with HAE [3].

Angioedema (AE) is a localized swelling of deep dermis and/or mucosa of the gastrointestinal or respiratory tract. This swelling is due to an increased vascular permeability ("from the Greek "angeio" –vessel- and "oedema" –swelling-). Regarding vascular permeability mastocyte is a main target cell located in skin. Provided with high affinity IgE receptors (FcεRI), mastocyte can be stimulated to release different substances with vasoactive potential (such as histamine, proteases, cysteinil leukotrines...) due to binding to sensitized IgE or antibodies generated secondary to autoimmune conditions [4]. On the other hand, bradykinin due to its vasoactive function is a very important molecule, clue in some forms of AE. Factor XIIa produces kallicrein and kallicrein is able to produce bradykinin from high molegular weight kininogens. It is important to know that the molecule responsible of the inhibition of this metabolic chain (both the factor XII and the kallicrein) is C1-Inhibitor (C1-Inh) [4]. Then, it is easily understandable that a C1-Inh deficiency or an increase in activity or amount of kallicrein or factor XII can lead to AE.

Although the syndromic diagnosis is usually easy, the etiological diagnosis can be challenging. A precise diagnosis is important for an adequate management. In this sense, Bork et al described that mortality in patients with HAE who had not been diagnosed was 29% *vs* 3% in patients who had been diagnosed [5].

Classification of AE

There are different criteria to classify AE. AE can be classified based on the familial history as Hereditary or Acquired (Table 1). When hereditary form is suspected, the next step is to distinguish if it exists a C1-Inh deficiency (HAE I and II) or not (HAE III). Among acquired forms there are several causes; the precise diagnosis depends on medical history. However, the etiology is often not found (idiopathic) [6]. From a therapeutical point of view, it can be more useful a classification based on the pathophysiology as histaminergic and non-histaminergic forms (Table 2), being non-histaminergic forms not associated to urticaria manifestations and usually responsive to antihistamines [4,7].

Non-Histaminergic angioedema

Hereditary C1-Inh Deficiency: HAE type I and II: It presents an autosomal dominant inheritance [8]. The pathological key is the lack of C1-Inh activity. It is explained by a quantitative reduction of C1-Inh (HAE type I –representing 85% of HAE-) or by a qualitative reduction of C1-Inh activity, being not able to inhibit C1 estearase (HAE type II –representing 15% of HAE on average-). Genetic alterations of both forms are different and heterogeneous and located in the gen SERPING1 [8]. Type II HAE mutations are usually located in the active position of the enzyme (aminoacyd 444), whereas type I HAE mutations are most variables [9]. In any way, the final result is the lack of kallicrein inhibition, resulting in an overproduction of bradykinin.

Acquired C1-Inh Deficiency: AAE type I and II: As in the hereditary form, there is a lack of C1-Inh activity. However, in these cases there is not a family history or a genetic mutation. It was firstly described by Caldwell in 1972 [10] in the context of a patient with lymphoma. Similar to HAE, there are two forms. Type I: C1-Inh is catabolised faster than normally [11]. An anti-idiotype response against an immunoglobuline is produced; anti-idiotype-idiotype binding creates an immunocomplex that produces an excess of C1 activation and subsequent excess of C1-Inh catabolism [12]. Type

Table 1: Classification of main types of angioedema.

TYPES OF ANGIOEDEMA			
HEREDITARY		ACQUIRED	
C1-Inh Deficiency	NON C1-Inh Deficiency	C1-Inh Deficiency	NON C1-Inh Deficiency
HAE type I HAE type II	HAE type III	AAE type I AAE type II	Allergic By drugs Physical urticaria Urticarial vasculitis Related to eosinophilia Idiopathic

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Table 2: Histaminergic *vs* Non-histaminergic AE.

	Histaminergic	Non-histaminergic AE	Unknown
Associated urticarial	Yes	Non	Yes
Pathophysiology	Histamine and other molecules from mast cell	Bradykinin system	---
Conditions	Acquired AE non related to C1-Inh deficiency	C1-Inh Deficiency (hereditary and acquired) HAE type III ACE inhibitor-induced AE	Idiopathic
Response to antihistamine, corticoid, adrenaline	Yes	No	Variable

II: C1-Inh can present normal or higher level than normally but it is inactivated (dysfunctional C1-Inh protein) [13].

Clinical differences between HAE and AAE are subtle. However, some data can be of interest in differential diagnosis. HAE is usually manifested in the first two decades of life instead of AAE, in which age of onset depends on associated pathology [14]. Limbs are a frequent location of AE in HAE, whereas in AAE face is a more frequent location [15]. Abdominal pain is reported more frequently in HAE (nearly 80% of cases) [14] than in AAE (30-50% of cases) [14,15]. As clinical characteristics are not sufficiently specific, complementary tests are necessary (Table 3).

HAE type III ("HAE non related to C1-Inh deficiency"): It was described in 2000 by two independent groups [16,17]. As HAE I and II, there is a familial condition but no alterations in components of complement system or mutation at C1-Inh gen level (SERPING 1) were found (Table 3) [16,17]. Initially HAE III was reported only in women, generally in relation with pregnancy, hormonal contraception/therapy or oestrogen replacement therapy. Subsequently, although low frequent, families with male cases have been reported [18,19]. Pathogeny seems to focus in coagulation factor XII gene mutations and polymorphisms in aminopeptidase P –APP- and angiotensin I-converting enzyme –ACE- (both responsible of bradykinin degradation) [20,21]. The mutations in factor XII gene result in increase of factor XII activity and polymorphisms in APP and ACE associated result in low of activity of these two enzymes [20,21]. All changes lead to an increased amount of bradykinin, final responsible of the development of AE.

Although the reason of female predominance of clinical manifestation is not absolutely clarified, some data support the idea of an influence due to gender. So, oestrogen suppresses ACE expression [22] and increases bradykinin concentrations [23,24]. On the other hand, although the effect of oestrogen on APP activity is unknown, a recent report suggests that androgens increase APP levels [25]; as androgens and oestrogens have generally antagonistic effects, it can be hypothesized that oestrogens might reduce APP activity.

Secondary to ACE inhibitors/angiotensin II receptor blockers (ARB): ACE is responsible of bradikinin catabolism [26,27]. So, inhibition of ACE leads to bradikinin elevation. It should be noted that whereas AE secondary to deficiency of C1-Inh and type III HAE show a bradikinin augmentation due to increase of production, in this case the augmentation is due to a degradation deficiency. Onset is usually after few weeks of the drug intake [28]; however, cases manifested several months after have been described [29].

Cough and AE are well known as adverse effects of ACE inhibitors. ARB was presented as an alternative because it acts directly inhibiting angiotensin II receptor, avoiding the adverse effects of ACE inhibitors. However, in 1995 the first case of AE related to losartan was described [30]. After, they were described other cases related to ARB and the cause was not understood [31]. In the last years it has been proved that ARB can elevate the level of bradikinin [32].

Histaminergic angioedema

Allergic angioedema: It is a reaction mediated by IgE as response to different antigens. Main related antigens are food, penicillin derivatives, insect bites, and radiocontrast. It is generally manifested few hours after the exposition [4].

Secondary to NSAID: NSAID can produce AE due to pharmacodinamic effects instead of by allergic effect. Inhibition of cyclooxigenase 1 (COX-1) leads to a derivation of arachidonic acid metabolism to lipooxigenase path. So, it occurs an overproduction of leucotrienes. However, selective inhibitors of COX-2 are well tolerated [33].

Episodic angioedema with eosinophilia (Gleich's syndrome): It is a rare entity described by Gleich in 1984 [34]. Its clinical features are recurrent episodes of AE, urticaria, pruritus, fever and increased of weight. Furthemore, patient shows a marked hypereosinophilia and IgM increased [35,36]; an increase of IgE has also been described [37]. Prognosis is good, without visceral involvement (conversely to hypereosinophilia syndrome) and good response to low doses of systemic corticoids [38,39].

It is hypothesized a T-helper lymphocytes stimulation that could secrete different cytokines, as IL-5 and 6 leading to chemotaxis and activation of eosinophils [40-42]. After this activation, eosinophils produce major basic protein and eosinophil cationic protein,

Table 3: Complementary test for differential diagnosis of hereditary and acquired angioedema.

	Level of C1-Inh	Function of C1-Inh	Level of C4	Level of C1q	Mutation
HAE I	Low	Normal	Low	Normal	SERPING 1
HAE II	Normal/Elevated	Altered	Low	Normal	SERPING 1
AAE I	Low	Normal	Low	Generally low	None
AAE II	Low	Altered	Low	Genereally low	None
HAE III	Normal	Normal	Normal	Normal	FXII

Note: Other forms of angioedema do not affect complement system values.

responsible of inflammatory reaction and fluid extravasation (manifested as angioedema and gain of weight) [34,39].

Atopic condition, parasite infection, malign diseases and other condition related to hypereosinophilia (hypereosinophilic syndrome, phylariasis, NERDS syndrome, eosinophilia-myalgia syndrome, eosinophilic fasciitis or Churg-Strauss syndrome) must be discarded.

Non episodic angioedema related to eosinophilia: It is characterized by angioedema and eosinophilia. It was differentiated from the previous condition by Chikama et al [43]. It is a clinical picture more frequent in Japan, where it has been described mostly in women between 20-40 years [43]. Conversely to Greich's syndrome, there is no high fever or recurrence of episodes and eosinophilia is lower [44], showing self-resolution [45].

Other forms of AE: associated with physical urticarias and with cholinergic urticarial and associated with contact urticarial [4].

Idiopathic chronic angioedema

Often, after an adequate clinical research no cause is found and AE is classified as idiopathic. However, some authors signal possible etiologies responsible of idiopathic AE. Leznoff et al in 1983 [46] suggested an association between urticaria/AE and thyroid autoimmunity. After, there have been multiple studies supporting this hypothesis [47-50]. These studies showed a statistically higher number of individuals with thyroid autoimmunity at analytical level than in group of individuals without chronic urticaria/AE. Subsequently, hormonal therapy has been proved in refractory cases of urticaria/AE showing clinical response [51]. Other authors have shown the presence of antibodies against high-affinity IgE receptors and others against IgE [52,55], producing immunocomplexes that activate high-affinity IgE receptors of mastocytes. In these cases, degranulation of mastocytes occurs without the presence of a specific antigen.

Urticarial vasculitis (UV)

UV can be clinically manifested as angioedema [42% according to Mehregan et al] [56]. It happens when vasculitic process involves capillaries and postcapillary venules of deep dermis or subcutaneous tissue [57]. Other manifestations of UV are systemic symptoms related to vasculitis or manifestations related to specific conditions related to UV [systemic lupus, Sjögren syndrome, leukemia, infections…] [58]. If UV is suspected, biopsy is necessary. It must be said that UV is not consider a form of urticaria nowadays because of the different pathophysiology [59].

Clinical Manifestations

Clinical manifestations are based on oedema, which can be located at both mucosae and deep dermis. At mucosal level the symptoms depends on the location: abdominal pain, even abdominal occlusion (digestive system), respiratory distress (respiratory tract) or other less common manifestations as cerebral edema or pleural effusion. When AE occurs at mucosal level the diagnosis can be really challenging. However, when oedema occurs at cutaneous level the diagnosis becomes easier. Cutaneous AE is characterized by swelling of the skin with ill-defined edges and burning sensation (more than pruritus), conversely to urticarial lesions that show well defined edges and the main symptom is pruritus [4].

In a retrospective study including 875 patients from Emergencies Department, the most important epidemiological data were gathered [6]. It was described an incidence predominance of female (66.8%) *vs* male (33.2%). Regarding the race, blacks were the most affected (59.1%). AE secondary to ACE inhibitors was the most frequent cause (56.6%), followed by allergic AE (21.4%) and idiopathic (16.3%). In this study the risk factors associated with more severe cases (requiring admission +/- intubation) were age (over 63.0 +/- 15.8 years), white Hispanic race, ACE inhibitors consumption, ASA class of III or above, cardiopulmonary disease and positive smoking history.

Diagnosis

A thorough medical history is mandatory for an adequate diagnosis. As it has been commented above, AE symptoms are different from those of urticaria. So, burning sensation is more frequent than pruritus and if lesions are in non-distensible areas pain is characteristic. Also, AE lasts longer than urticaria (several days' *vs* less than 24 hours) [4]. Due to mucosal involvement of AE, symptoms related to digestive system and respiratory tract must be asked and taken into account. Familial history is very important (HAE). Regarding personal history, systemic conditions (diseases related to UV, neoplasms related to AAE) or drugs (NSAID, ECA inhibitors, ABR...) that could be related to AE must be gathered, also as previous history of AE or urticaria, time of evolution and frequency of episodes. An early onset suggests a hereditary form, being puberty a common age of onset of HAE secondary to deficiency of C1-Inh and HAE type III. Precipitating factors, such as traumatisms [as dental manipulation] [60,61], drugs, conditions related to estrogens [pregnancy, menstruation, contraceptives, hormonal therapy] [62], or infections [63.64] are also a valuable information for diagnosis and management.

At physical examination, it can be found a swollen lesion that can be deforming (especially in face), with not well defined edges and without high temperature (conversely to inflammatory-infectious conditions). Urticarial wheals can be associated, suggesting a histaminergic form of AE. Airway and oral mucosa must to be examined to rule out respiratory involvement. Because of systemic manifestations related to AE, constitutional syndrome must to be kept in mind and lymphatic nodes explored. Based on medical history, complementary tests can be requested such as: CBC (evaluating leukocytes number and leukocyte formula –note that eosinophilia can be related to Gleich's syndrome, non episodic AE associated to eosinophilia, parasitic infestation…); level of C4, level and activity of C1-Inh (Table 3); other complementary tests based on analytical and clinical suspects (chest radiograph if lymphoma is suspected, cutaneous biopsy if UV is suspected, mutation of factor XII if HAE-III is suspected…).

Treatment

Obviously, respiratory distress and/or hemodynamic alteration must be addressed with preference. Differential diagnosis between histaminergic and non-histaminergic AE is very important (Table 2); AE with urticaria generally responds well to antihistamines, conversely to AE secondary to an excess of bradykinin (non-histaminergic AE) [7].

In relation with the indications of therapy, it should be noted that

an acute episode does not need a therapeutic intervention always. If the episode is of low intensity and involves not life-threatening areas it can be sufficient an expectant attitude or managed with oral tranexamic acid [65]. However, episodes involving head and neck, even if they are of low intensity, should be treated always because of the risk of a rapid progression to laryngeal obstruction [66].

Histaminergic AE

Different authors [4,67] recommend a progressive therapeutic protocol. The first step corresponds to non sedating antihistamines. The second step is a combination of non sedating antihistamines and sedating antihistamines. When therapy is still no effective additional drugs are associated to antihistamines. According to autoimmune hypothesis, cyclosporine has shown to be effective in a dose range of 2.5-4 mg/kg/day in cases in which an underlying autoimmune condition can be present [68]. So, 80% of patients had a complete or almost complete response and after stopping the drug 2/3 of patients maintained the response or the symptoms were adequately controlled with antihistamines. Other therapeutic possibilities are methotrexate, sulfasalizine, hydroxychloroquine, colchicine, mycophenolate mofetil, azathioprine or cyclophospyhamide [59]. Regarding systemic corticoids, prolonged use is not recommended. So, they are recommended only few days at low doses (20-40 mg/day) when acute and severe episodes are presented. It should be noted that in this therapeutic strategy the objective is not necessarily the complete elimination of the symptomatology but the reduction of pruritus and urticaria to "functionally acceptable" levels [67,68].

In some patients where standard therapy is not effective, antimicrosomal/antitiroglobuline antibodies and hypothyroidism are present. In these cases Heymann [69] recommends the administration of levothyroxine at an initial dose of 1.7 micrograms/kg/day. If there is no response after 8 weeks of treatment, it must be suspended. If there is a positive response, the treatment must be maintained 1-2 months after clinical remission and recurrences could be retreated with levothyroxine.

In the case of AE associated to hypereosinophilia, low doses of systemic corticoids are usually effective [44,45].

Bradykinin mediated angioedema

Hereditary and Acquired C1-Inh Deficiency: If AE is clinically established the best option is a substitutive therapy with C1-Inh derived from plasma. It is effective for treatment and prophylaxis [70-73]. Recently, Icatibant (antagonist of receptor 2 of bradykinin) [74] and Ecallantide (antagonist of kallicrein receptor) [75] have been shown as an effective treatment for acute attack. Observational studies suggest a faster and better response of AE episode if C1-Inh is taken sooner [76,77]. It is possible that the same phenomenon occurs with Icatibant and Ecallantide; however, the experience is limited.

Regarding the prophylaxis, it can be performed at "short term" when prophylaxis is necessary before the exposure to specific situations such as dental extraction, oral surgery, intubation or other interventions involving areas at high risk for AE development. In "short term" prophylaxis, C1-Inh is the best option. However, if C1-Inh concentrate is available and the patient will be admitted for a minor intervention, it is possible an expectant attitude and C-Inh1 will be administered only if necessary. If C1-Inh concentrate is not available "short term" prophylaxis can be performed with attenuated androgens or antifibrinolytics 5 days before the intervention and 2-5 days post-intervention. If patient will be admitted for a major intervention or intubation prophylaxis is necessary, it must be performed in any case [73,78].

"Long-term" prophylaxis is indicated when episodes are frequent and/or severe, an episode of severe abdominal pain or AE at head/neck level [73]. In HAE, attenuated androgens are more effective than antifibrinolytics [79]; however, in AAE, antifibrinolytics (such as tranexamic acid) seem to be more effective [80].

HAE type III: It has been described the utility of C1-Inh as treatment of acute episode of AE [81]. Both corticoids and antihistamines have shown no efficacy [81]. Regarding the long-term prophylaxis, danazol (attenuated androgen) has shown its efficacy in different patients [82]. As other forms of bradykinin mediated AE, corticoids, antihistamines and tranexamic acid are not effective [82-84].

Bork et al have reported a similar sensitivity to oestrogens for the three forms of HAE [62]. So according to this, it can be hypothesized that an antiestrogen environment could be of benefit for HAE attack. In this sense, it has been reported a retrospective study showing that women with non-allergic AE taking progestin as contraceptive treatment suffered less number of AE attacks after than before the onset of the treatment. The benefit was higher in women taking a higher dose of progestin [85]. So, prospective studies evaluating the benefit of antigonadotropic progestin in the next years would be of interest.

ACE-inhibitor induced AE: Although drugs above commented for bradykinin mediated AE may have a rol in the acute episode, the most important is the discontinuation of the responsible medication. It should be noted that, although angiotensin II receptor antagonists had been proposed as a safe alternative, episodes of AE have also been described with this medication [31].

Finally, it should be commented Omalizumab (humanized monoclonal anti-IgE antibodies) as a promising drug in refractory and chronic urticaria and angioedema, as shows the randomized, placebo controlled study reported by Saini et al [86]. However, the high-cost is the main limitation for its use.

Conclusions

Although etiologic diagnosis of AE can be challenging, the task can become more accessible if the main causes of this condition and the main alterations of laboratory involved in AE are known. Furthermore, some key pathophysiology concepts are important both for understanding the different causes of AE and for understanding the new therapy that are developing at present. Prospective studies are needed to know the clinical benefit of the new drugs developed in the last years, such as Icatibant, Ecallantide or Omalizumab.

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