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Idiopathic histaminergic angioedema without wheals: a case series of 31 patients

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Summary

Idiopathic histaminergic acquired angioedema (IH-AAE) is a common cause of recurrent angioedema without wheals. It is a mast cell-mediated disease thought to belong to the same clinical entity as chronic urticaria (CU). The objective of this study was to describe the clinical and epidemiological characteristics of IH-AAE patients. From 2014 to 2015, 534 patients were seen at our national reference centre for angioedema and/or urticaria. Among them, we identified 31 patients with idiopathic histaminergic acquired angioedema without wheals (IH-AAE). Thirty-one patients (15 men and 16 women) with a mean age of 50 years met the criteria for IH-AAE. The average delay in diagnosis was 6·3 years. A history of allergy was found in 12 patients (38·7%), nine suffering from allergic rhinitis. The mean duration of attacks was 28·1 h. The AE attack was located in the upper respiratory tract in 54·8% of cases (17 patients). A lingual location was found in 29% of patients. Men were more likely than women to have an upper airway involvement. No intubations or admissions to intensive care units were reported. The dosage of anti-histamines to control the symptoms was onefold the recommended dose in 51·6% of patients (16 patients), twofold in 32% (10 patients) and three–fourfold in 16·1% (five patients). IH-AAE is characterized by an important delay in diagnosis, a frequent involvement of the upper airway and a benign course during attacks. As in CU, a trial of up to fourfold dose of H1-anti-histamines may be necessary to control symptoms.

Keywords: Allergy, Skin, Inflammation, Mast Cells

Introduction

Chronic urticaria (CU) is a highly prevalent condition characterized by the occurrence of hives and/or angioedema (AE) for at least 6 weeks [1]. Both symptoms are related to increased vasopermeability and vasodilation, in the dermis for the former and in the hypodermis for the latter. Hives manifest clinically as red or white, itchy and transient papules, whereas AE is a deep and self-limiting swelling of the hypodermis or the submucosal tissue [2].

In clinical practice, diseases can be classified into three categories: diseases with urticaria without AE, diseases with AE alone and conditions with both urticaria and AE [3,4].

In the subset of AE without urticaria, the aetiologies are varied. A recent expert consensus established the definitions of the disease entities involved in this group: three types of hereditary AE (HAE) have been identified (HAE with C1-inhibitor deficiency, HAE with FXII mutations and HAE of unknown origin) and four acquired forms of AE have been separated: idiopathic histaminergic AE (IH-AAE), idiopathic non-histaminergic AE (InH-AAE), acquired AE related to angiotensin-converting enzymes inhibitors (ACEi-AAE) and AAE with C1-inhibitor deficiency (C1-INH-AAE) [5]. In this way, a large survey involving 1056 patients in a tertiary reference centre identified 57% of patients diagnosed as bradykinin-mediated AE and 36% as idiopathic histaminergic acquired-AE (IH-AAE) [6]. The prevalence of IH-AAE may be even much higher in the general population, and probably the most common form of angioedema without urticaria [5].

Chronic urticaria and IH-AAE are thought to belong to the same clinical entity [5]. During the evolution of CU, 50% of patients exhibit both wheals and angioedema, and

Table 1. Diagnostic criteria for idiopathic histaminergic acquired angioedema according to the international recommendations of the Hereditary Angioedema International Working Group

1. Histamine-mediated angioedema characteristics [7]	1. Sudden, pronounced swelling of the lower dermis and subcutis 2. Sometimes pain rather than itching 3. Frequent involvement below mucous membranes 4. Resolution that is slower than for wheals and can take up to 72 h
2. Exclusion of specific causes of angioedema [5]	Causative agents of immediate hypersensitivity reactions Associated autoimmune/infectious disease C1 esterase inhibitor (C1-INH) deficiency, and mutation in factor XII
3. Efficacy of anti-histamines	Fifty per cent decrease in the frequency of symptoms following the introduction of the treatment with anti-histamines

approximately 10% experience only angioedema, meeting the criteria of IH-AAE [2,4,6].

The clinical characteristics of IH-AAE have been described as similar to those of chronic urticaria; however, the publications relating the features of this form of angioedema are lacking and the current data originate from discussions among experts [5].

Hence, the purpose of this study is to establish the clinical and epidemiological characteristics of patients suffering from IH-AAE.

Methods

We conducted a retrospective analysis of patients seen at our tertiary-level centre. During 2014–15, 534 patients were referred to our national reference centre for angioedema and/or urticaria. Among them, 31 presented angioedema without wheals. We then identified patients with angioedema who improved with anti-histamines. Medical history was obtained during specialized consultations at our centre. The data collected were: frequency, duration and site of the attacks, age at onset, history of allergy, use of an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) and use of non-steroidal anti-inflammatory drugs (NSAID). The AE characteristics reported in this study (location, duration) were those of the last AE attack and of all previous episodes before the first consultation at our centre. A complete physical examination was carried out for every patient.

The clinical criteria to make the diagnosis of IH-AAE were the ones proposed previously (Table 1) [5,7]. The response to anti-histamines was defined as a 50% reduction in the frequency of attacks. This criterion was considered as a confirmation yardstick and necessary for the diagnosis of IH-AAE in this study. A trial of up to a fourfold dose of second-generation H-1 anti-histamines was carried out for each patient. The efficacy assessment of the background treatment was made in systematic follow-up consultations.

When data were available on previous treatments of acute episodes, the efficacy criterion was an onset of symptom relief within 2 h.

We assayed serum thyroid-stimulating hormone (TSH) levels, D-dimers levels, protein concentrations of C1-inhibitor antigen, C4 and C1q by radial immunodiffusion. C1-inhibitor activity was measured with the chromogenic substrate Na-Benzoyl-L-arginine-ethyl-ester-hydrochloride (BAEe) [8]. Low C1-inhibitor levels were considered as an exclusion criteria.

All statistical analyses were performed using SPSS software version 20·0 (SPSS Inc., Chicago, IL, USA). Quantitative variables were summarized by mean ± standard deviation (s.d.) and compared by the Student's *t*-test or Mann–Whitney *U*-test when appropriate. Categorical data were summarized as count (%) and compared by χ^2 or Fisher's exact test when appropriate. Results were considered significant if the two-tailed *P* value was less than 0·05.

Results

Population characteristics

Thirty-one patients were referred to our centre for AE without wheals and met the criteria for IH-AAE: 15 men and 16 women, with a mean age of 50 years (Table 2). The mean age at diagnosis was 50 years and the average time to diagnosis was 6·3 years.

Twenty-three per cent of these patients had hypertension, and 12·9% had been diagnosed with type 2 diabetes. Five patients were receiving treatment with angiotensin-converting enzyme inhibitors (ACEi) and three with angiotensin receptor blockers (ARB). A previous diagnosis of either ACEi or ARB-induced bradykinin-mediated AE was reported in each of these eight cases. All patients receiving ACEi or ARB mentioned previous episodes of AE attacks before initiation of these treatments and no worsening of symptoms were reported afterwards. None of the diabetic patients had been prescribed gliptins, but three of them were receiving ARB. Twelve patients had a history of allergy (38·7%), nine suffering from allergic rhinitis and four from anaphylaxis to food allergens, drugs or wasp venom. The comorbidities recorded are shown in Table 2.

Eleven patients (35·4%) had a history of at least one episode of wheals before the period of AE attacks [median

Table 2. Demographic characteristics of idiopathic histaminergic acquired angioedema (IH-AAE) patients

Gender *n* (%)		
Men	15/31 (48·3%)	
Women	16/31 (51·7%)	
Age		
< 30	4/31 (12·9%)	
30–60	17/31 (54·8%)	
> 60	10/31 (32·2%)	
Comorbidities		Specific treatments
AHT	7/31 (23%)	ACE inhibitors: 5 patients perindopril: 2 enalapril: 2 ramipril: 1 Angiotensin receptor blockers: 3 patients candesartan: 2 valsartan: 1
Diabetes	4/31 (12·9%)	Gliptins: 0 patients
Asthma	4/31 (12·9%)	
Allergic rhinitis	9/31 (29%)	
Allergies – anaphylactic reactions	4/31 (12·9%)	
Drug allergy	1/31	
Food allergy	2/31	
Stinging insect venom allergy	1/31	
Autoimmune thyroiditis	1	
Other autoimmune diseases	0	
Oncological diseases	0	

ACE = angiotensin-converting enzyme; AHT = arterial hypertension.

time of 6 years (1–42) before the first AE attack]. Two patients experienced episodes of wheals after diagnosis (8 months and 2 years after diagnosis).

Biological characteristics

All patients had normal C1 esterase inhibitor (C1-INH) activity. Serum TSH levels were measured in 21 patients. This assay was within the normal range in 20 patients. One patient exhibited a low serum TSH level, related to the presence of anti-thyroperoxydase antibodies. Eight patients were assayed for serum D-dimer levels, two of whom presented concentrations above the normal range. In all cases, serum tryptase levels were within the normal range (mean serum tryptase 3·84 μg/l ± 1·91).

Location and characteristics of attacks

The face was the most frequent location of AE attacks, found in 80·6% of patients. Fifty-four per cent of patients had presented at least one attack in the upper respiratory tract, including oral mucosa (17 patients). A lingual location was found in 29% of cases and a laryngeal location in 3% (one patient).

Men were more likely to have an upper airway involvement (80%) than women (31·2%, $P = 0·011$). A peripheral involvement was noted in 35·4% of patients (11 patients) and 16% (five patients) presented swellings at the level of external genital organs. No deaths were recorded. The mean duration of attacks was 28·1 h (± 21.0) and the median was 24 h (Table 3). The mean frequency of attacks before diagnosis was 39·8/year (± 66·8), and the median 24/year.

Risk factors and factors precipitating attacks

In 41·9% of cases (13 patients), a factor facilitating the occurrence of AE attacks was identified. These factors were as follows: drugs for nine patients (morphine derivatives for one patient, antibiotic treatment for two patients and

Table 3. Characteristics of attacks

Mean age of the first attack	43·8 years
Average delay in diagnosis	6·3 years
Location of attacks *n* (%)	
Upper airway	17 (54·8)
Tongue	9 (29)
Larynx	1 (3)
Face/perioral	25 (81)
Limbs	11 (35·4)
Abdominal	0
Genital organs	5 (16·1)
Attack frequency	
< 15 per year	10 (32·2)
15–30 per year	14 (45·2)
> 30 per year	7 (22·6)
Median duration of attacks h (range)	24 (2·5–84)

Table 4. Treatment modalities of angioedema attacks prior to the diagnosis of idiopathic histaminergic acquired angioedema (IH-AAE)

Referral to an emergency room *n* (%)		15/31 (48)
Treatments used for the acute attack, prior to the diagnosis of IH-AAE		Reported efficiency *n* (%)
Anti-histamines	$n = 3$	3 (100)
Corticosteroids	$n = 7$	0
Association of anti-histamine with corticosteroids	$n = 10$	6 (60)
Icatibant	$n = 1$	0

NSAID for six patients), physical exertion (one patient), pressure urticaria (one patient) and episodes of infection (two patients).

Management of the attack

During the last acute episode [before, 48% of patients (17 patients)] were referred to emergency departments. Patients referred to an emergency room had an upper airway involvement in 73·3% of cases (11 of 15 patients) *versus* 37·5% (six of 10) in patients who were not. This difference was not statistically significant ($P = 0{\cdot}073$). Data on the treatment modalities were available for 21 patients: three patients were treated with anti-histamines, seven with corticosteroids and 10 with an association of corticosteroids and anti-histamines. Anti-histamines were efficient in 100% of cases, corticosteroids in no cases and the association in 60% of patients.

One patient was treated with the bradykinin receptor antagonist icatibant with no improvement. Efficacy data are shown in Table 4.

Dosage of H1-anti-histamine to achieve the clinical response

All patients were prescribed a continuous anti-histamine treatment. The dosage of anti-histamines to prevent subsequent attacks was onefold the recommended dose in 51·6% of patients (16 patients), twofold in 32% (10 patients), threefold in two patients and fourfold in three patients. There were no statistical differences in terms of frequency or location of attacks between patients treated with a high dose (three–fourfold) and a standard dose of anti-histamines.

Discussion

IH-AAE is thought to be the main form of angioedema without wheals [5]. This is not surprising, as approximately 10–20% of the population will one day experience an episode of urticaria [4], and given that 10% of these patients present AE without wheals [2,4,6]. Indeed, it has been suggested that chronic urticaria and IH-AAE belong to the same clinical entity [5]. Surprisingly, before this study no data were available relating to the epidemiological and clinical characteristics of the patients suffering from IH-AAE. Some differences with CU may be highlighted. In this series the sex ratio was balanced (15 men and 16 women), whereas in patients suffering from CU a female preponderance is commonly described, with an average female to male ratio of 2 : 1 [9]. The mean age of the first attack was 43·8 years, as described previously in epidemiological studies on CU (average age 40 years) [10]. The apparently high rate of diabetic patients in this case series (12·9%) probably reflects the higher prevalence in this age group (average age of 50 years). Interestingly, the AE attacks were located frequently in the upper airway (54·8% of patients reported such a location) including one patient with a laryngeal location. Despite the threatening presentation of these patients no fatalities occurred, and all patients recovered without requiring admission to an intensive care unit. To our knowledge, unlike in patients with bradykinin-mediated AE, no deaths have ever been reported in patients suffering from CU with upper airway involvement.

The main differential diagnosis of IH-AAE is bradykinin-mediated AE. During the acute phase, no clinical characteristics may help to differentiate between the two entities. Short duration of attacks (a few hours) would argue in favour of IH-AAE [11]. In this series, however, the median duration of symptoms was 24 h, still consistent with the diagnosis of bradykinin-mediated AE. A history of spontaneous urticaria separately from the current episode of AE would be an argument in favour of IH-AAE. In this work, however, 58% of patients had not experienced any episode of urticaria before diagnosis.

Five patients were on treatment with ACEi and three with ARB, leading initially to the wrong diagnosis of ARB or ACEi-induced bradykinin-mediated AE (ACEi-AE). In this series one patient was prescribed the bradykinin receptor antagonist icatibant. This probably reflects the difficulty for clinicians to make the diagnosis of histaminergic-AE in certain situations. Thus, a suspicion of ACEi-AE may lead correctly to the prescription of specific treatments for bradykinin-mediated AE, because of the potential severity of this type of AE.

With regard to the background treatment, this series supports the benefit of a higher dosage of anti-histamines in some patients to achieve the clinical response [12–14]. Indeed, prescribing anti-histamines up to fourfold has been shown to improve chronic urticaria symptoms without increasing side effects such as somnolence in approximately three-quarters of patients [14]. Astonishingly, during the acute episode, treatment with corticosteroids alone was not efficient in seven patients and the association of corticosteroids and anti-histamines seemed less efficient

than anti-histamines alone. According to our experience, the lack of response to this association is unusual. It must be emphasized that the low number of patients (only three patients treated with anti-histamines alone) and the retrospective nature of this study do not allow any conclusion regarding treatment efficacy. For acute exacerbations, anti-histamines and a short course of corticosteroids may indeed be considered, as recommended in patients with CSU [7]. However, given that corticosteroids might have no effect for 4–6 h, their usefulness during the acute phase needs to be clarified, and placebo-controlled studies are still lacking [15,16]. For long-term prophylaxis, corticosteroids are not recommended in patients with CSU, due to obligatory side effects and to the risk of development of severe anti-histamine-resistant forms of the disease [7,17]. We suggest that the same therapeutic approach may be beneficial for IH-AAE, given the similarity of these diseases.

The diagnosis criteria used in this study were those published previously [5]. Given the important prevalence of IH-AAE among patients presenting with recurrent AE, we suggest that an empirical treatment with anti-histamines could be used as a diagnostic test. However, as in patients with CU, one can assume that some mast cell-mediated AE may be resistant to anti-histamines, requiring third-line therapies such as omalizumab or cyclosporin [7]. By definition, using the current criteria of IH-AAE, anti-histamine-resistant mast cell-mediated AE were excluded from this study. Thus, the patients suffering from the most resistant forms of the disease are not described in this series. However, according to our experience, resistance to anti-histamines in histamine-mediated AE patients remains exceptional.

Other limits of this study are inherent in its retrospective nature, in particular recall bias regarding previous episodes of wheals and/or AE and their treatments. Prospective studies would be necessary to confirm the data presented here.

Conclusion

IH-AAE is a common cause of recurrent AE without wheals. This form of AE remains often unrecognized and an important delay in diagnosis is observed. The diagnostic approach is exclusively clinical. An upper airway involvement occurred in half of patients, with a benign course in all cases. A background therapy with an increased dosage up to fourfold of second-generation anti-histamines may be required to control the symptoms.

Disclosure

There are no disclosures to declare.

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