

Recurrent Angioedema: Occurrence, Features, and Concomitant Diseases in an Italian Single-Center Study

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Keywords

Angioedema · Autoimmunity · Bradykinin · Complement deficiency · Lymphoproliferation · Serum complement activity

Abstract

Background: Angioedema (AE) is a potentially life-threatening condition with hereditary (HAE), acquired (AAE), or iatrogenic causes. A careful workup allows for the identification of the etiology of attacks and the appropriate management. In this cohort study, based on a clinical practice setting, we aimed at investigating clinical and laboratory findings concerning different features of patients with recurrent AE who were referred to a single, tertiary-level center for HAE. **Methods:** Clinical and laboratory data of patients fulfilling the criteria for C1-inhibitor-deficient HAE (C1-INH-HAE), C1-INH-AAE, angiotensin-converting enzyme inhibitor-related AE (ACEI-RA), and idiopathic AAE (I-AAE) were evaluated. Descriptive statistics were analyzed by means of the Mann-Whitney U test. The Fisher exact test was used for group comparisons. **Results:** Patients were diagnosed with type 1 HAE ($n = 14$), type 2 HAE ($n = 1$), C1-INH-AAE ($n = 8$), ACEI-RA ($n = 16$), or I-AAE ($n = 26$). We included only patients with concomitant autoimmune diseases from the I-AAE group ($n = 8$, aut-I-AAE).

Age at disease onset and at diagnosis was younger in type 1 HAE than in all the other groups. The diagnostic delay was longer in type 1 HAE than in ACEI-RA. C4 and C1q levels were lower in C1-INH-AAE than in type 1 HAE, ACEI-RA, and aut-I-AAE. Both HAE and C1-INH-AAE showed lower C1-INH antigen and function compared to the other groups. Peripheral attacks were more frequent in type 1 HAE, while airway, abdominal, and oral attacks were prevalent in C1-INH-AAE. **Conclusion:** Investigating the clinical and laboratory features of recurrent AE without wheals represents a major topic for facilitating early diagnosis and improving treatment strategies for this heterogeneous and misdiagnosed condition.

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Introduction

Recurrent angioedema (AE) is a potentially life-threatening condition with hereditary (HAE), acquired (AAE), or iatrogenic causes [1, 2]. The new classification describes 3 types of HAE (a genetic deficiency of C1-inhibitor [C1-INH], normal C1-INH with factor XII mutations, and of unknown origin) and 4 types of AAE (C1-INH, nonallergic angiotensin-converting enzyme inhibitor [ACEI]-related, and idiopathic [histaminergic or nonhistaminergic]).

gic)) [3, 4]. HAE and AAE due to C1-INH deficiency, i.e., C1-INH-HAE and C1-INH-AAE, are diseases characterized by potentially fatal attacks of subcutaneous and submucosal edema of the upper airways, face, abdomen, and extremities. This phenomenon results from an inadequate control of the generation of bradykinin [5–9]. Diminished C1-INH is the hallmark of C1-INH-HAE (types 1 and 2) due to mutations in the C1-INH gene (*SERPING1*) that result in deficiency or functional impairment of C1-INH [10]. The deficiency in C1-INH in C1-INH-AAE does not depend on genetic defects but on protein consumption [11]. It is well known that C1-INH-AAE is frequently associated with lymphoproliferative diseases and/or anti-C1-INH inactivating autoantibodies, and patients with C1-INH-AAE present with a higher risk than the general population for B cell malignancies [12, 13–15]. Diagnosis of C1-INH-HAE and C1-INH-AAE may be troublesome; suspicion and knowledge of these diseases are therefore crucial for early diagnosis [16]. A common cause of recurrent AAE is ACEI treatment; patients who develop AE during this treatment most likely have an altered metabolism in which bradykinin episodically accumulates in the plasma [17, 18]. Even though recurrent AE is a well-documented side effect of ACEI treatment, its features still frequently go unrecognized, which may lead to an extensive workup before clinical recognition [11].

International consensus on the management and treatment of patients with C1-INH-HAE and C1-INH-AAE has improved diagnostic delay and outcome [10, 19]. However, guidelines concerning diagnostic and therapeutic strategies are yet to be defined in non-C1-INH-deficient AE, both hereditary (type 3 HAE) and nonhereditary (ACEI-RA and I-AAE) [3, 20–23]. Moreover, recurrent I-AAE may be related to or associated with autoimmune conditions, but exploring whether there is a causal link or it is an epiphenomenon deserves further investigation [24, 25].

In this cohort study, based on a clinical practice setting, we investigated different forms of recurrent AE without wheals, in order to give an overview of the findings concerning different features from consecutive patients referred during the last 3 years to a single, tertiary-level center for HAE.

Material and Methods

Between 2012 and 2015, a total of 89 consecutive patients with AE without wheals were evaluated at our reference center for HAE. Clinical and laboratory records were collected in a database. We examined the medical records of patients who fulfilled the manda-

Table 1. Diseases detected in 17 of 26 I-AAE patients

Associated disease	n	%
Infections	5	29.4
<i>Helicobacter pylori</i>	3	60
<i>Entamoeba histolytica</i>	1	20
Hepatitis B virus	1	20
Autoimmune disorders	8	47.1
Connective-tissue diseases ^a	2	25
Psoriasis	1	12.5
Autoimmune thyroiditis	5	62.5
Other diseases	4	23.5
Primary hypogammaglobulinemia	2	50
Goiter and benign thyroid nodules	2	50

^a Sjögren syndrome (n = 1); Raynaud phenomenon (n = 1).

tory criterion of recurrent AE unaccompanied by urticaria that can be categorized as follows:

- HAE: subcutaneous, noninflammatory, self-limiting AE with serum levels of C1-INH antigen or function <50% of normal. Type 1 HAE was diagnosed when both the antigenic and functional levels of C1-INH were low; type 2 was diagnosed when the functional levels of C1-INH were low and the antigenic levels were normal or high [26, 27].
- C1-INH-AAE: the C1-INH deficiency was based on the presence of AE that was identical to HAE with measurements of serum C1-INH antigen or C1-INH function <50% of normal. Unlike HAE, however, the deficiency of C1-INH does not depend on genetic defects but on protein consumption, with onset during or after the 4th decade of life and the absence of a family history of AE [11, 15, 28].
- ACEI-RA: AAE with normal C1-INH in patients (with no other cause of AE) in whom AE recurred during ACEI therapy and disappeared upon withdrawal of ACEI [29].
- aut-I-AAE: recurrent AE in patients with concomitant autoimmune disorders, otherwise idiopathic.

We excluded patients with AE (42/89) related to specific allergic factors (allergic AE, 24/42, 57%), or defined as I-AAE (18/42, 43%). The clinical and laboratory records of 47 patients were thus analyzed. Clinical data included a family history of AE, age when initial symptoms appeared, age at diagnosis, sites of the attacks, concomitant disorders and therapies, and on-demand and prophylactic treatment.

Laboratory assays examined C3, C4, quantitative and functional C1-INH, and C1q levels. Measurements of serum C3 and C4 were obtained by means of nephelometric assays: normal values were 90–180 and 10–40 mg/dL for C3 and C4, respectively. Serum C1q and C1-INH antigen levels were measured with radial immunodiffusion while functional C1-INH assessment was performed from the citrate plasma by a chromogenic method. Normal values were 15.4–35.1 mg/dL and 70–130% for quantitative and functional C1-INH, respectively, and 50–250 mg/L for C1q.

The study was approved by the local ethics committee and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to inclusion in the study.

Table 2. AE without wheals according to clinical characteristics in 47 patients

	HAE I	HAE II	C1-INH-AAE	ACEI-RA	aut-I-AAE
Patients, <i>n</i> (%)	14 (30)	1 (2)	8 (17)	16 (34)	8 (17)
Male:female ratio	1	n.a. ^a	1	3*	0.33
Age at onset, years					
Median (range)	15.5 (4–27)**	n.a. ^a	61 (43–71)	63.5 (46–80)	46.5 (25–65)***
Mean ± SD	16.21±9.17**	n.a. ^a	58.63±9.55	61.81±10.97	47±14.28***
Age at diagnosis, years					
Median (range)	20 (4–79) [§]	n.a. ^a	63 (47–74)	63.5 (48–81)	53 (38–66) ^{§§}
Mean ± SD	27.43±23.79 [§]	n.a. ^a	61.38±10.21	64.31±10.28	52.4±10.77 ^{§§}
Diagnostic delay, years					
Median (range)	0.5 (0–54)	n.a. ^a	2.5 (1–5)	1 (0–6) [†]	2 (0–15)
Mean ± SD	11.21±17.35	n.a. ^a	2.75±1.75	1.88±2.03 [†]	5.38±5.96

The Mann-Whitney U test was used to compare variables and the Fisher test to analyze prevalence; $p < 0.05$ was considered significant). HAE I, type 1 hereditary angioedema; HAE II, type 2 hereditary angioedema; C1-INH, C1 inhibitor; AAE, acquired angioedema; ACEI-RA, angiotensin-converting enzyme inhibitor-related angioedema; aut-I-AAE, idiopathic acquired angioedema with concomitant autoimmune diseases; n.a., not applicable. * $p = 0.03$ vs. aut-I-AAE. ** $p < 0.0001$ vs. C1-INH-AAE, ACEI-RA, and aut-I-AAE. *** $p = 0.01$ vs. ACEI-RA. [§] $p = 0.001$ vs. C1-INH-AAE; $p < 0.0001$ vs. ACEI-RA; $p = 0.01$ vs. aut-I-AAE. ^{§§} $p = 0.02$ vs. ACEI-RA. [†] $p = 0.03$ vs. HAE I; $p = 0.04$ vs. aut-I-AAE.

^a Female sex; age at onset, 16 years; age at diagnosis, 38 years; diagnostic delay, 16 years.

Statistical Analysis

Quantitative variables were expressed as median ± range and mean ± standard deviation (SD). Continuous variables were compared using the Mann-Whitney U test. Contingency analyses were performed with the χ^2 test or the Fisher exact test, where appropriate. Statistical analysis was considered significant when two-tailed p values were < 0.05 . All data were stored on a server and statistical analyses were performed using GraphPad Prism software v6.0.

Results

In a 3-year period, HAE was diagnosed in 15 patients (32%): type 1 HAE occurred in 14 (93.3% of the HAE patients) belonging to 10 unrelated families, while type 2 occurred only in 1 (6.7% of the HAE patients). C1-INH-AAE was detected in 8 patients (17%). An additional group including 8 patients was classified as aut-I-AAE (17%). A hematological disease occurred in 5/8 (62.5%) of the C1-INH-AAE patients; 2 cases were monoclonal gammopathy of uncertain significance, 2 were marginal B lymphoma, and 1 was type II cryoglobulinemia. In the other C1-INH-AAE cases, a solid cancer (of the uterus, esophagus, or kidney) was detected. ACEI-RA was diagnosed in 16 patients (34%), during treatment with ACEI for hypertension in all of them. The median age of the patients at the beginning of ACEI treatment was 63 years (range 43–80 years). The median duration of ACEI ther-

apy before symptom onset was 6 months (range 1–36 months); AE appeared during the 1st month of therapy in 3 patients (18.7%). We registered a median timing of measurement of C1-INH in relation to age at initiation of ACEI treatment of 18 months (range 1–204 months). Autoimmune conditions were reported in 30.7% (8/26) of patients with I-AAE (Table 1). Associated diseases were detected in 34.6% (9/26) of the other I-AAE patients (Table 1). The male-to-female ratio was similar in all the groups, except for the ACEI-RA group with a ratio that was significantly higher than the aut-I-AAE group ($p = 0.03$; Table 2).

Age at Onset and Diagnostic Delay

Type 1 HAE patients were younger at disease diagnosis than those with C1-INH-AAE ($p = 0.001$), ACEI-RA ($p < 0.0001$), and aut-I-AAE ($p = 0.01$; Table 2). Similarly, age at disease onset was younger in type 1 HAE than in the other 3 groups ($p < 0.0001$); patients with ACEI-RA were older at disease onset than aut-I-AAE patients ($p = 0.01$; Table 2).

The diagnostic delay in type 1 HAE was similar to in the other groups, being significantly higher only when compared to ACEI-RA ($p = 0.03$). ACEI-RA patients had a lower diagnostic delay than aut-I-AAE patients ($p = 0.04$). There was no difference in diagnostic delay between C1-INH-AAE and aut-I-AAE patients.

Table 3. Complement parameters in the study population

	HAE I	HAE II	C1-INH-AAE	ACEI-RA	aut-I-AAE
C3, mg/dL					
Median (range)	105 (84.2–135)**	n.a. ^a	108.5 (42.6–160)	127 (111–157)	86.2 (89.2–120)***
Mean ± SD	106.4±17.64**	n.a. ^a	105.6±37.54	129.8±13.69	100.4±14.27***
C4, mg/dL					
Median (range)	6.14 (0.01–22.2)*	n.a. ^a	1.5 (1.5–5.43) [#]	26.55 (18.3–40.8)	20.1 (8–30.8) ^{##}
Mean ± SD	7.45±5.8*	n.a. ^a	2.58±1.63 [#]	26.96±6.61	19.8±7.38 ^{##}
C1-INH antigen, mg/dL					
Median (range)	5.6 (3.6–8) [‡]	n.a. ^a	4.5 (4–25.2) ^{††}	28.15 (19.5–32.5)	22.85 (18.5–35.1)
Mean ± SD	5.51±1.16 [‡]	n.a. ^a	8.2±7.27 ^{††}	27.18±3.99	25.2±6.12
C1-INH function, %					
Median (range)	26.45 (10–43.4) [†]	n.a. ^a	16.5 (3.8–7.3) ^{††}	106 (76.6–137)	106.4 (78–120.8)
Mean ± SD	26.61±7.31 [†]	n.a. ^a	23.85±22.84 ^{††}	106.6±18.1	100.7±16.1
C1q, mg/L					
Median (range)	117 (100–170)	n.a. ^a	26.46 (5–48.46) [§]	129.7 (100.5–156)	139.7 (108–190)
Mean ± SD	124.4±21.83	n.a. ^a	27.95±17.89 [§]	127.2±15.4	140.9±27.12

The Mann-Whitney U test was used to compare variables; $p < 0.05$ was considered significant. C1-INH, C1 inhibitor; HAE I, type 1 hereditary angioedema; HAE II, type 2 hereditary angioedema; AAE, acquired angioedema; ACEI-RA, angiotensin-converting enzyme inhibitor-related angioedema; aut-I-AAE, idiopathic acquired angioedema with concomitant autoimmune diseases; n.a., not applicable. * $p < 0.0001$ vs. ACEI-RA; $p = 0.0003$ vs. aut-I-AAE. ** $p = 0.004$ vs. ACEI-RA. *** $p = 0.001$ vs. ACEI-RA. [#] $p = 0.03$ vs. HAE I; $p < 0.0001$ vs. ACEI-RA and aut-I-AAE. ^{##} $p = 0.03$ vs. ACEI-RA; [‡] $p < 0.0001$ vs. ACEI-RA and aut-I-AAE; ^{††} $p < 0.0001$ vs. ACEI-RA; $p = 0.0002$ vs. aut-I-AAE. [†] $p < 0.0001$ vs. ACEI-RA and aut-I-AAE. ^{††} $p < 0.0001$ vs. ACEI-RA and aut-I-AAE. [§] $p < 0.0001$ vs. HAE I, ACEI-RA, and aut-I-AAE.

^a C3: 88.9 mg/dL; C4: 3 mg/dL; C1-INH antigen: 32.5 mg/dL; C1-INH function: 3%; C1q: 120 mg/L.

Complement System

Complement parameters from the study population are summarized in Table 3 and reported in online supplementary Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000453663). C3 levels were lower in both type 1 HAE and aut-I-AAE than in ACEI-RA ($p = 0.004$ and $p = 0.001$, respectively). C4 levels were lower in C1-INH-AAE than in type 1 HAE ($p = 0.03$), ACEI-RA, or aut-I-AAE ($p < 0.0001$ for both comparisons). Moreover, patients with type 1 HAE had lower C4 levels than ACEI-RA ($p < 0.0001$) and aut-I-AAE patients ($p = 0.0003$), and aut-I-AAE patients had lower C4 levels than ACEI-RA patients ($p = 0.03$). C1-INH antigen and function were similar in type 1 HAE and C1-INH-AAE. However, both type 1 HAE and C1-INH-AAE showed lower C1-INH antigen and function with respect to the other groups ($p < 0.0001$ for all comparisons). C1q levels were more reduced in C1-INH-AAE than in type 1 HAE, ACEI-RA, and aut-I-AAE ($p < 0.0001$ for all comparisons; Table 3).

Sites of Attacks and Treatment Provided

Abdominal attacks were more prevalent in C1-INH-AAE than in ACEI-RA ($p = 0.03$), while peripheral attacks

were more frequent in type 1 HAE than in ACEI-RA ($p = 0.03$). Inversely, airway attacks were more prevalent in C1-INH-AAE than in type 1 HAE ($p = 0.04$). The prevalence of oral attacks was lower in type 1 HAE than in C1-INH-AAE ($p = 0.0004$), ACEI-RA ($p < 0.0001$), and aut-I-AAE ($p = 0.0004$) (Fig. 1). The type 2 HAE patient experienced both abdominal and peripheral attacks. Attacks that required airway management or abdominal surgery, with an uncertain diagnosis, were not registered in our study cohort.

In type 1 HAE patients with frequent attacks and in whom on-demand therapy was inadequate to achieve adequate control of the disease, regular therapy to prevent AE episodes was considered. Approximately half of the type 1 HAE patients (42.8%) were administered continuous prophylaxis with tranexamic acid (66.6%) or attenuated androgens (33.4%); the type 2 HAE patient was treated with tranexamic acid in continuous prophylaxis. In all these HAE patients, the frequency and severity of AE attacks diminished. The on-demand C1-INH concentrate was available for all the HAE patients (types 1 and 2) and for half of the C1-INH-AAE patients, with clinical efficacy. Therapy of C1-INH-AAE included the treatment of the associated disease.

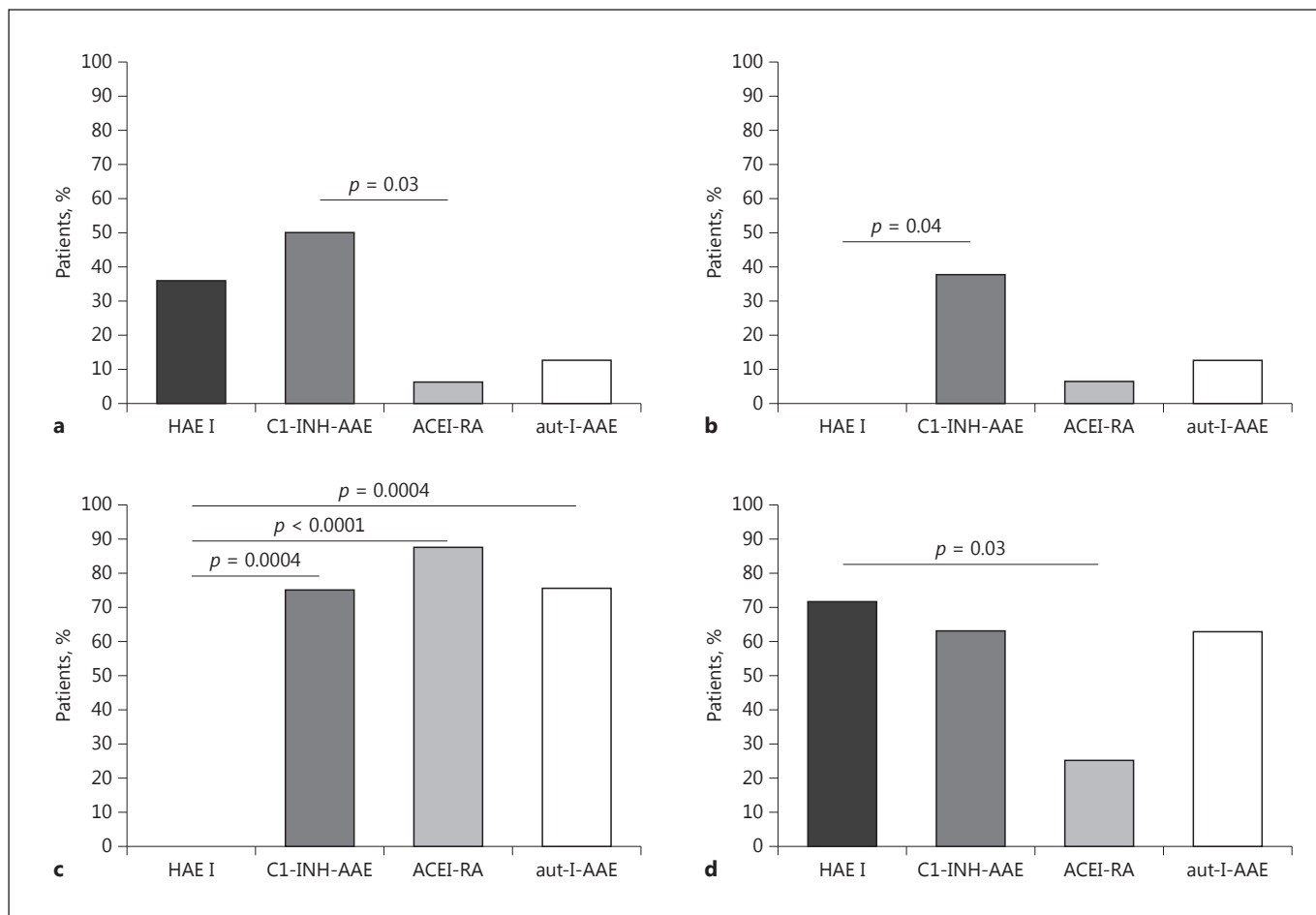


Fig. 1. Prevalence of acute attacks according to the sites of recurrent AE in our study population. HAE I, type 1 hereditary angioedema; C1-INH, C1 inhibitor; AAE, acquired angioedema; ACEI-RA, angiotensin-converting enzyme inhibitor-related angioedema; Aut-I-AAE, autoimmune idiopathic acquired angioedema. **a** Abdominal attacks. **b** Airway attacks. **c** Oral attacks. **d** Peripheral attacks. Prevalences were compared by using the Fisher exact test ($p < 0.05$ was significant).

In all the ACEI-RA patients, AE disappeared upon withdrawal of ACEI and none of the patients relapsed after this discontinuation of treatment. All aut-I-AAE patients were put on long-term antihistamine therapy, for a minimum of 1 month; in 75%, AE disappeared or was drastically reduced.

Discussion

In clinical practice to date, diagnosing recurrent AE represents a tricky challenge that often remains confined within the syndrome of urticaria, and is commonly considered an “allergic” condition [28]. However, AE has

been reported as the most frequent cause of hospital admission among all acute, allergic, nonasthmatic diseases [30]. We thus investigated different forms of recurrent AE, unaccompanied by wheals, in consecutive patients referred during the last 3 years to the outpatient clinic of our tertiary-level center. A comprehensive familial and personal history, potential triggers, and specific tests allowed us to relate the AE to the exposure to external agents (foods and environmental allergens) in 24 of 89 patients (16%).

Further investigations were tailored to the individual findings. Whenever patients reported a history of recurrent, nonhistaminergic, subcutaneous, or upper airway AE and/or abdominal-pain attacks of unknown etiology,

C1-INH deficiency was taken into account [31]. The possibility of this deficiency was strongly suggested by clinical key features and family history. The estimated prevalence of C1-INH-HAE in the general population is set at 1/50,000 [32]. However, a recent nationwide survey of C1-INH-HAE prevalence in Italy provided a minimum prevalence of 1/64,935 [27]. The frequency of HAE in patients with AE without urticaria is still unknown. In our series, HAE was diagnosed in 15 patients (16.8%), although being a reference center for the diagnosis and treatment of HAE probably biased this percentage [28].

C1-INH-AAE was diagnosed in 9% of the total number of patients with recurrent AE. This prevalence may certainly have been affected by a selection of patients directly referred to a tertiary-level center for HAE. In our series, half of the C1-INH-AAE patients had a diagnosis of hematological disease. In addition, 37.5% of the C1-INH-AAE patients showed both reduced levels of C1-INH and a solid malignancy (of the uterus, kidney, or esophagus). In this context, little is known about the relationship between AE and solid malignancy to date [33, 34], while cancers such as lymphoma or leukemia were recently listed as the second-most common cause of AE death after HAE [35]. It was recently reported that almost 30% of patients with C1-INH-AAE have or will develop non-Hodgkin lymphoma, and that clonal B cell proliferation represents a condition underlying AAE which leads to the production of autoantibodies against C1-INH and then to non-Hodgkin lymphoma [36]. Moreover, C1-INH deficiency in lymphomas can also be asymptomatic and appears to respond to immunochemotherapy [37]. In our cohort of C1-INH-AAE, all of the patients followed a specialized workup according to their individual pathologic condition (hematological or oncological). Neutralizing autoantibodies against C1-INH are thought to play a major role in C1-INH-AAE [38]. However, in our study cohort, we did not measure anti-C1-INH antibodies. To date, there is no sufficient understanding of the formation of anti-C1-INH antibodies or the correlation between these antibodies and disease outcome in AAE patients [38]. In this context, the detection of the neutralizing anti-C1-INH antibodies represents an intriguing future challenge in order to better explore the relationship between antibody production and the clinical features of C1-INH-AAE.

It is reported that an average 0.5–1% of patients taking ACEI may develop AE, a well-documented but still frequently unrecognized side effect of these drugs [11]. The incidence of ACEI-RA can be affected by its feature of remitting and relapsing which can confound clinical recognition and lead to an extensive workup. Moreover,

some cases of patients with mild reactions who present to primary care in an outpatient setting often go unreported [39]. It has been reported that the risk of death associated with ACEI-RA is higher for black people [35]. Moreover, ACEI-RA accounts for one-third of AE cases in the emergency room, but guidelines on treatment strategy for this group are yet to be defined [40]. Recent results from a randomized trial support the efficacy of the bradykinin receptor B2 antagonist (icatibant) in ACEI-RA in improving the time of the complete resolution of edema, in comparison with a combination therapy with glucocorticoids and antihistamines [41].

Recurrent AE in patients with no identified cause (I-AAE) was diagnosed in 20.2% of the whole AE cohort. However, we included only I-AAE patients with concomitant autoimmune diseases, given the relationship between complement system and autoimmunity [25, 42–44]. In view of this, it could be intriguing to explore the clinical and immunological features of aut-I-AAE patients. In our I-AAE cohort, an elevated proportion of patients (30.7%) had an associated autoimmune disease compared to the normal population [45]. However, the prevalence of I-AAE patients in the whole study group (8/89, 9%) was only slightly higher than in the general population. Moreover, 62.5% of the aut-I-AAE patients had autoimmune thyroid disorders, representing a prevalence of 5.6% in the whole cohort. Clinical associations between urticarial/recurrent AE and autoimmune thyroid disease [24, 46], connective-tissue disorders, and systemic vasculitis are reported in the literature [47, 48]. Defining a cause-effect relation between autoimmune disease and AE is still difficult. Our findings may support the hypothesis of a connection between the 2 conditions, but we cannot provide additional evidence and this issue remains controversial [19, 49]. Of note, 5 I-AAE patients had infections, thus highlighting the importance of screening for infectious foci when no obvious cause of AE can be detected [28].

The median age at disease onset was lowest in the HAE group. This was to be expected, given the effect of genetic defects on disease outcome and features [50]. In the type 1 HAE patients, there was a younger median age at diagnosis than for all the other patients; these data may be biased by the patients being referred to an AE reference center [28].

When evaluating the diagnostic delay, type 1 HAE patients had a delay of 11.5 years, consistent with recent data from the literature [32]. In addition, this delay was higher only with respect to the ACEI-RA group. In ACEI-RA patients, symptoms may appear early or several years af-

ter beginning ACEI therapy, which makes the diagnosis more difficult. In our cohort, the diagnostic delay turned out to be short, probably due to the selection of patients referring directly to an AE reference center; the median was 2 years, which differs slightly from recent data in the literature [51].

As expected, C1-INH antigen and function were similar in type 1 HAE and C1-INH-AAE, and were lower in HAE and C1-INH-AAE than in all the other groups. However, C4 and C1q levels were lower in C1-INH-AAE than in type 1 HAE, ACEI-RA, and aut-I-AAE. These results support the role of the measurement of serum C1q in the early differentiation between the 2 forms of C1-INH-related AE, i.e., C1-INH-AAE and type 1 HAE, representing a key challenge in laboratory tests for the diagnosis of AAE [52].

In our study cohort, type 1 HAE patients had a prevalence of peripheral sites for acute attacks, in accordance with the literature [53]. However, we did not register attacks on the airways in this group, probably due to the long-term treatment with both prophylaxis and on-demand therapy and the good disease control that is attained at an HAE reference center. Moreover, abdominal, airway, and oral attacks are known to be more frequent in C1-INH-AAE than in type 1 HAE and ACEI-RA, supporting a potential relationship between clinical severity and serum levels of the complement components [25]. In ACEI-RA the prevalent site of attacks was the oral cavity/tongue, in accordance with data from the literature [54].

Treatment of acute attacks in C1-INH-AAE, as in HAE, was based on replacement therapy using C1-INH concentrate and B₂-receptor blocker [19] with clinical efficacy. Prophylaxis with attenuated androgens (danazol) and tranexamic acid were effective in all the HAE patients who were continuously being treated for symptoms [16]. H₁-receptor blockers were effective in 75% of the aut-I-AAE patients. In addition, we registered a subgroup of patients with aut-I-AAE (25%) who were nonresponders to H₁-receptor blockers, and were probably affected by nonhistaminergic I-AAE [11]. In the literature, it has been reported that nonhistaminergic I-AAE patients appear to have similar clinical features and response to treatment with antifibrinolytic agent tranexamic acid as those who are deficient in C1-INH, suggesting that this form of I-AAE could have a pathogenetic mechanism similar to that of C1-INH-HAE and C1-INH-AAE, with bradykinin as the key mediator of the symptoms [55]. However, to date, the etiology of nonhistaminergic I-AAE remains unclear [11].

Despite the available clinical and laboratory tools, the diagnosis of recurrent AE remains a challenge. It is important to identify a C1-INH deficiency in both HAE and AAE because the management is completely different from that of non-C1-INH-mediated AE. The importance of laboratory testing in the diagnostic workup of recurrent AE has increased with the introduction of novel treatment strategies. AAE can benefit from the same clinical testing of HAE because most cases involve reduced levels of C1-INH [52]. Moreover, serum C1q assessment aids the early differentiation between AAE and HAE [52]. Recent evidence suggests novel laboratory methods for the differential diagnosis of AAE and HAE when the determination of C1-INH is not yet available [56]. There is widespread agreement on therapeutic goals (i.e., to reduce mortality and morbidity, reduce the frequency of attacks, improve quality of life, and train patients in self-administration) in C1-INH-related AE whereas no guidelines are available concerning the treatment of ACEI-RA and I-AAE [22, 23, 57–59].

Although our study cohort was small, by using a clinical practice setting in a single, tertiary-level center for HAE, we provide proof of the different features of recurrent AE without wheals that benefit from a complement screening, along with the analysis of clinical data for early differentiation and adequate treatment strategies. However, a future challenge, in a larger population, will be to explore the role of complement components in non-C1-INH-deficient recurrent AE, i.e., aut-I-AAE and ACEI-RA, and to create a better definition of C1-INH-AAE in nonhematologic conditions.

Disclosure Statement

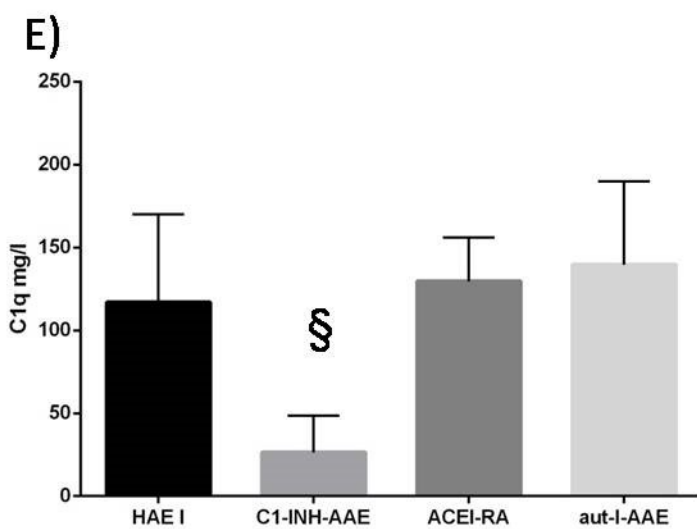
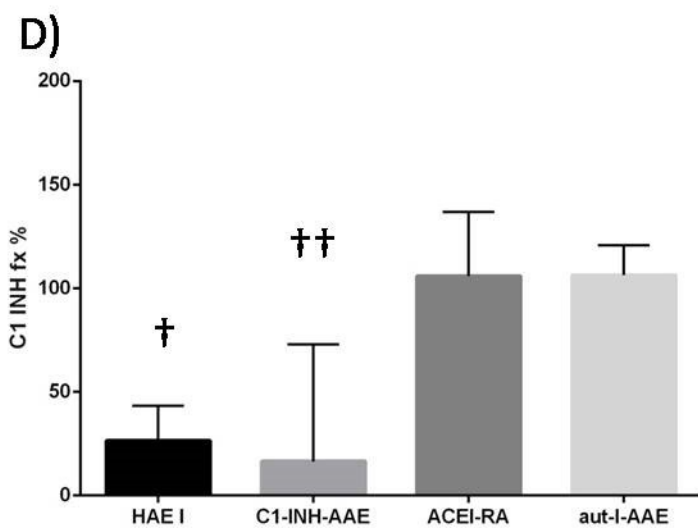
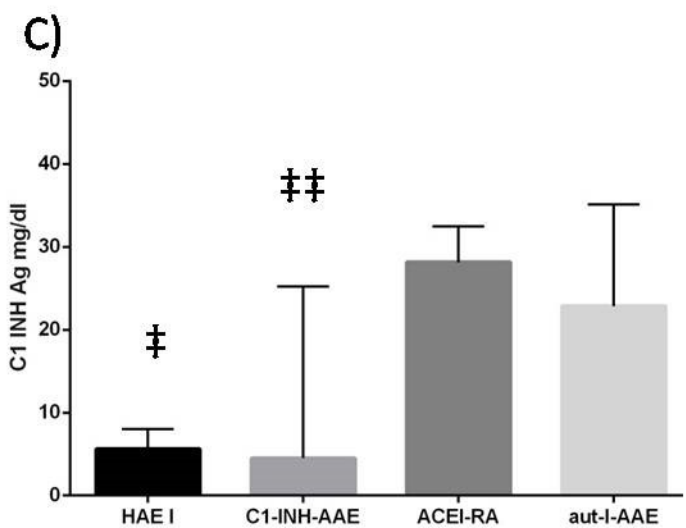
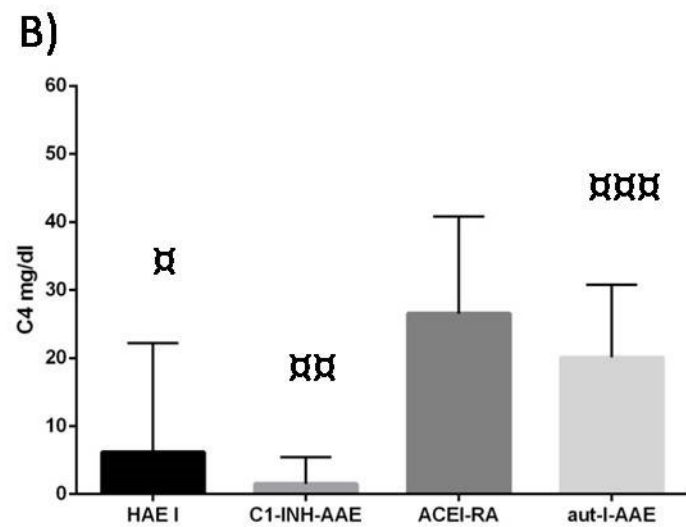
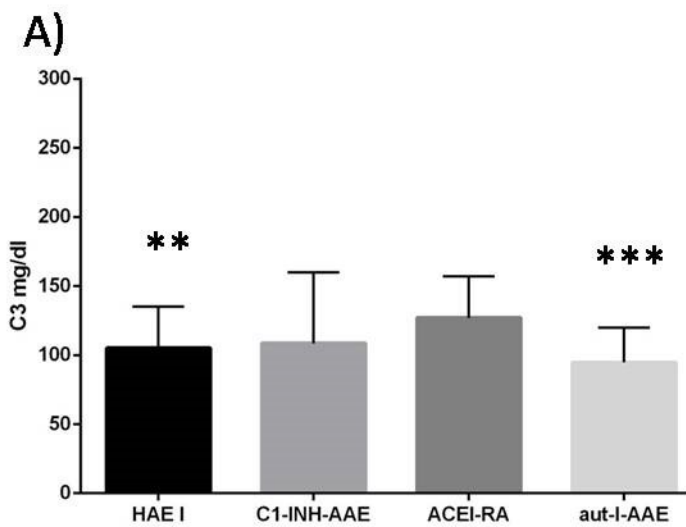
The authors declare they have no conflicts of interest.

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Suppl. Fig. 1. Complement parameters in the study groups. HAE I: type 1 hereditary angioedema; C1-INH: C1 inhibitor; AAE: acquired angioedema; ACEI-RA: angiotensin converting enzyme inhibitor related angioedema; aut-I-AAE: idiopathic acquired angioedema with autoimmune diseases; C1-INH Ag: C1 inhibitor antigen; C1-INH fx: C1 inhibitor functional. Data were expressed as median and range. Differences between values were analyzed using Mann-Whitney U test ($P < 0.05$ as significant). Panel A: C3 levels; ** $P = 0.004$ vs ACEI-RA; *** $P = 0.001$ vs ACEI-RA. Panel B: C4 levels; α $P < 0.0001$ vs ACEI-RA, $P = 0.0003$ vs aut-I-AAE; $\alpha\alpha$ $P = 0.03$ vs HAE I, $p < 0.0001$ vs ACEI-RA and aut-I-AAE; $\alpha\alpha\alpha$ $P = 0.03$ vs ACEI-RA. Panel C: C1 inhibitor antigen levels; $\ddagger$ $P < 0.0001$ vs ACEI-RA and aut-I-AAE; $\ddagger\ddagger$ $P < 0.0001$ vs ACEI-RA, $P = 0.0002$ vs aut-I-AAE. Panel D: C1 inhibitor functional levels; $\dagger$ $P < 0.0001$ vs ACEI-RA and aut-I-AAE; $\dagger\dagger$ $P < 0.0001$ vs ACEI-RA and aut-I-AAE. Panel E: C1q levels; $\S$ $P < 0.0001$ vs HAE I, ACEI-RA, and aut-I-AAE.