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Clinical profile of idiopathic angioedema based on severity and treatment response is independent of the presence of concomitant wheals

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Abstract

Background: Idiopathic angioedema varies in disease severity and treatment response, possibly due to different pathophysiological mechanisms. The presence of wheals is an indicator for histamine-mediated angioedema. Idiopathic angioedema patients are treated in accordance with chronic spontaneous urticaria guidelines. Little is known about treatment effectiveness in idiopathic angioedema patients without wheals in comparison to idiopathic angioedema patients with concomitant wheals.

Objective: To describe the disease severity profile in patients with angioedema of unknown cause in relation to prophylactic treatment and the presence or absence of concomitant wheals.

Methods: In this retrospective cohort study, all records of angioedema patients visiting the outpatient clinic of the UMC Utrecht between January 2015 and March 2020 were screened. Patients with idiopathic angioedema, including those with concomitant wheals, were included. Attack frequency, patient-reported disease control and attack treatment as indicator for severity were analysed in relation to prophylactic treatment at follow-up and outcomes were compared between patients with and without concomitant subordinary wheals.

Results: Two hundred thirty-six patients were included: 95% (139/236) with angioedema only and 41% (97/236) with angioedema and concomitant subordinary wheals. No prophylactic treatment was prescribed in 27% (64/236), with well-controlled disease in 86% (25/29) of patients. Antihistamine monotherapy was used in 59% (139/236) of patients and resulted in well-controlled disease in 68% (62/92). Add-on treatment was prescribed in 14% (33/236) of patients, omalizumab in 9% (22/236) specifically, with complete response in 38% (6/16) of patients and low attack frequency in another 18% (3/16). Difficult-to-treat disease was seen

in 8% (18/236), with no response to a fourfold dose of antihistamines or omalizumab. All findings were independent from the presence of concomitant wheals.

Conclusion: Angioedema is well manageable in the majority of patients without prophylactic therapy or antihistamine monotherapy, but a substantial proportion does not respond to antihistamines and/or omalizumab. Treatment response was independent of the presence or absence of concomitant wheals.

KEYWORDS

angioedema, bradykinine, histaminergic, wheals

INTRODUCTION

Angioedema (AE) is characterised by acute and transient localised swelling of the subcutaneous and mucosal tissue, affecting preferentially the facial and oropharyngeal area, the extremities and genitalia. The clinical presentation, natural course, severity and treatment response differ between and within patients.[1]

The pathophysiology of AE is not fully understood, but generally, two vasoactive peptides are thought to mediate acute AE swellings; namely, histamine and bradykinin, which both can lead to increased vascular permeability.[2] Hereditary angioedema (HAE), acquired C1 inhibitor deficiency (AAE-C1-INH) and angiotensin-converting enzyme inhibitors induced angioedema (ACEI-AE) are considered as bradykinin-mediated AE,[2] for which treatment is based on restoring C1-INH plasma levels and regulating the production of bradykinin.[2] Histamine-mediated AE is classified as acquired AE (AAE) and is associated with chronic spontaneous urticaria (CSU).[3] An estimated 33%–67% of CSU patients suffer from both (subordinary) wheals and AE.[4] Therefore, the presence of wheals in AE patients is currently an indicator for CSU diagnosis. Following CSU guidelines, after exclusion of C1-INH deficiency, ACEI-AE or urticarial vasculitis,[5,6] prophylactic treatment of AAE patients with or without wheals starts with antihistamine monotherapy up to a fourfold daily dose. In daily practice, these patients are classified into idiopathic histaminergic AAE (IH-AAE) and idiopathic non-histaminergic (Inh-AAE) AAE based on their clinical response to antihistamine therapy.[7] The next treatment step in antihistamine refractory patients is add-on treatment with omalizumab (anti-IgE).[3] When additional therapy with omalizumab is not effective, treatment alternatives are sparse.

Currently, little is known about the effectiveness of omalizumab in patients with idiopathic AE. The working mechanism is not fully understood[7] and data are based on case studies with, in total, only 30 individual patients, which describe the complete response in 57% and partial response in 43% of idiopathic AE patients without wheals.[8,9] Overall, in previous studies, therapeutic response to prophylactic AE treatment is based on attack frequency.[10–13] To obtain a more complete perspective on the disease severity, it is important to also take into account the patient's perspective on the disease and the required attack treatment as an indicator of the attack severity.

The primary aim of this study is to describe the profile of idiopathic AE, both histaminergic and non-histaminergic, in a large population of patients by assessing the attack frequency, patient-reported disease control and attack severity in relation to the prescribed prophylactic treatment including add-on therapy and to investigate whether there is a difference between idiopathic AE patients with or without concomitant wheals.

MATERIAL AND METHODS

Study design and population

A retrospective cohort study was performed at the University Medical Centre Utrecht (UMCU). All patients with a diagnosis related to AE who visited the outpatient clinic of the Dermatology/Allergology, Otorhinolaryngology, Haematology, Rheumatology and Internal Medicine departments between 1 January 2015, and 1 March 2020, were selected and screened for inclusion. Patients were included when they were diagnosed with idiopathic AE without (AE-only) or with concomitant subordinary wheals (AE-wheals). Patients were excluded, when the AE was induced by a specific trigger such as known allergy, ACE inhibitor use or when AE due to C1-INH deficiency (hereditary or acquired) was proven. To avoid selection bias

concerning treatment response, patients without at least one follow-up visit and a follow-up duration less than 90 days were excluded. The complete selection process is presented in Supporting Information: Figure S1. The local medical ethics committee declared that WMO approval was not required (protocol number 20-327).

All data were extracted from the electronic patient records. Cohort characteristics and disease history (eg affected location, treatment history) were collected from the first visit. The maximum prophylactic treatment prescribed between first visit and follow-up was categorised as 'none', 'antihistamine monotherapy' and 'add-on treatment' including, montelukast, omalizumab and tranexamic acid.

After maximum prophylactic treatment was prescribed, the outcome measures were collected at follow-up. Attack frequency and intensity of attack intervention were collected as indicators of AE severity. Attack frequency was categorised as 0 attacks; <1 to 1 per year; 1 per 6 months to 1 per 2 months; at least 1 per month. The intensity of attack intervention was categorised as: (1) 'not needed'; (2) 'oral rescue medication' including antihistamines, corticosteroids or tranexamic acid; (3) parenteral rescue medication such as 'adrenalin'; (4) 'urgent care' including a visit (and treatment received) at the emergency room or hospitalisation in intensive care unit. Patient-reported disease control was categorised as (1) 'complete control' (no symptoms); (2) 'good control' (minimal symptoms; no impairment); (3) 'partial control' (improvement, but still substantial impairment); (4) 'no improvement' (substantial impairment). Data regarding attack frequency, patient-reported disease control and attack treatment was not available for all patients and availability was different for the three outcome measures.

Statistical analysis

Statistical analyses were performed by using IBM SPSS Statistics 25.0.0.2. Graphs were produced using GraphPad Prism 8.3 and Microsoft Excel. Comparison between two groups was made by *t* test or Mann–Whitney *U* test for continuous variables that are normally or non-normally distributed, whereas the one-way analysis of variance (ANOVA) or Kruskal–Wallis were used for comparison between three groups. Comparisons of categorical variables were made by the χ^2 test in case of two groups and the Fisher–Freeman–Halton exact test was used in case of three groups.

TABLE 1 Cohort characteristics

	Total (n = 236) (*n* = 236)	AE-only[b] (*n* = 139)	AE-wheals[c] (*n* = 97)
Female (%)	161 (68%)	93 (67%)	68 (70%)
Age (years)	46 (15–90)	**48 (16–85)**[*]	**43 (15–90)**
Affected locations			
Facial and neck area	209 (89%)	122 (88%)	87 (90%)
Face	71 (30%)	45 (33%)	26 (27%)
Ear	3 (1%)	3 (2%)	0 (0%)
Eye	100 (42%)	60 (43%)	40 (41%)
Lip	148 (63%)	**74 (54%)**[**]	**74 (76%)**
Cheek	42 (18%)	28 (20%)	14 (14%)
Neck	11 (5%)	9 (7%)	2 (2%)
Oral area, pharynx, larynx	146 (62%)	90 (65%)	56 (58%)
Tongue	102 (43%)	**70 (50%)**[***]	**32 (33%)**
Throat	76 (32%)	38 (27%)	38 (39%)
Oropharynx	11 (5%)	6 (4%)	5 (5%)
Larynx	3 (1%)	2 (1%)	1 (1%)
Peripheral	56 (24%)	30 (22%)	26 (27%)
Abdominal	10 (4%)	5 (4%)	5 (5%)
Urogenital	11 (5%)	6 (4%)	5 (5%)
Other[a]	8 (3%)	6 (4%)	2 (2%)
Unknown	1 (0.4%)	0 (0%)	1 (1%)

Note: Significant differences between AE-only and AE-wheals patients are marked bold.

Abbreviation: AE, angioedema.

[a]Chin, nose.

[b]Angioedema patients without wheals.

[c]Angioedema patients with wheals.

*0.046; **<0.001; ***0.011.

RESULTS

In total, 236 patients (68% female; mean age 46 years) were confirmed to have idiopathic AE with a median follow-up time of 30 months. The majority of patients (*n* = 139; 59%) had idiopathic AE without wheals (AE-only) and 41% (*n* = 97) idiopathic AE with concomitant subordinary wheals (AE-wheals). Patient characteristics are shown in Table 1. AE-only patients were significantly older and suffered more often from tongue

swelling and dysphonia compared to AE patients with wheals (Table 1).

Prophylactic treatment strategy: The majority of patients respond to antihistamine monotherapy

At first presentation, 64% ($n = 139$) of patients reported a high attack frequency of at least 1 attack per month, which was reported significantly more often in AE-wheals patients compared to AE-only patients ($p = 0.001$, $n = 69$; 78% and $n = 70$; 54%, respectively).

Only 39% ($n = 92$) of patients in our cohort used prophylactic treatment at first presentation. This was increased during follow-up to 73% ($n = 172$) of patients. The maximum prescribed prophylactic treatment (required for disease control) during follow-up could be differentiated into three strategies: 27% ($n = 64$) of patients with no prophylactic treatment; 59% ($n = 139$) with antihistamine monotherapy and 14% ($n = 33$) with add-on treatment. AE-wheals patients received prophylactic treatment with antihistamines or add-on treatment more often compared to AE-only patients (Table 2).

When analysing attack frequency at follow-up, patients without prophylactic treatment reported no attacks in 86% ($n = 25$, out of 29 with available data). Only 14% ($n = 4$) of patients reported AE attacks at follow-up (Figure 1A; Supporting Information: Table S1). Of these four patients, one used oral rescue medication, two patients sought urgent care and one did not report having used any rescue medication during follow-up. Studying patient-reported disease control at the end of follow-up: 87% ($n = 26$, out of 30 with available data) of patients without prophylactic treatment experienced complete or good control of disease (Figure 1B; Supporting Information: Table S1).

Patients with antihistamine monotherapy (in any dose) reported no attacks at follow-up in a considerably lower percentage: 46% ($n = 42$, out of 92 with available data). Low attack frequency (<1 per year to 1 per 2 months) was reported by 22% ($n = 20$) of patients and even high attack frequency (at least 1 attack per month) was reported by 33% ($n = 30$) of patients (Figure 1A; Supporting Information: Table S1), indicating relatively poor disease control in the antihistamine monotherapy group at follow-up based on attack frequency. Looking at patient-reported disease control at the end of follow-up, 77% ($n = 89$, out of 116 with available data) of patients with antihistamine monotherapy reported complete or good control of disease (Figure 1B; Supporting Information: Table S1).

Studying the effectiveness of a fourfold daily dose of antihistamines, specifically, this was prescribed in 41% ($n = 96$) of patients during follow-up. Complete remission (0 attacks) or a low attack frequency (<1 per year to 1 per 2 months) was seen in 64% (40% and 24%, respectively; $n = 43$ out of 68 with available data) at follow-up. Thirty-six percent ($n = 25$) of patients continued to suffer from high attack frequency with at least one attack per month. Response to fourfold daily dose antihistamines was independent of the presence of wheals.

Add-on treatment was prescribed to 14% ($n = 33$) of patients during follow-up (Table 2), of which omalizumab was most often used; 9% ($n = 22$) of cases. Further analysis of therapeutic response was only performed for omalizumab patients. Data about specific attack frequency at follow-up was available for 16 patients using omalizumab; 38% ($n = 6$) of patients experienced no attacks and 18% ($n = 3$) reported low attack frequency (1 per 6 months to 1 per 2 months), but 44% ($n = 7$) at least one attack per month (Figure 1A; Supporting Information: Table S1).

However, based on patient-reported disease control at the end of follow-up, 35% ($n = 7$ out of 22) of all patients treated with omalizumab reported complete or good disease control after the addition of omalizumab to antihistamine treatment, while 65% ($n = 13$) of patients had partial or no disease control, suggesting high burden, also in patients with relatively low attack frequency.

TABLE 2 Maximum prescribed prophylactic treatment during follow-up

Maximum prophylactic treatment	Total ($n = 236$)	AE-only[a] ($n = 139$)	AE-wheals[b] ($n = 97$)	p Value
None	64 (27%)	54 (39%)	10 (10%)	<0.001
Antihistamine monotherapy	139 (59%)	73 (53%)	66 (68%)	0.017
1–2 fold dose	38 (16%)	22 (16%)	16 (17%)	
3–>4 fold dose	101 (43%)	51 (37%)	50 (51%)	
Add-on treatment	33 (14%)	12 (9%)	21 (22%)	0.005
Montelukast	6 (3%)	1 (1%)	5 (5%)	
Omalizumab	22 (9%)	9 (6%)	13 (13%)	
Tranexamic acid	5 (2%)	2 (1%)	3 (3%)	

Note: Maximum prophylactic treatment at follow-up was defined as the maximum prophylactic treatment prescribed between the first and last visit before data lock.

Abbreviation: AE, angioedema.

[a]Angioedema patients without wheals.

[b]Angioedema patients with wheals.

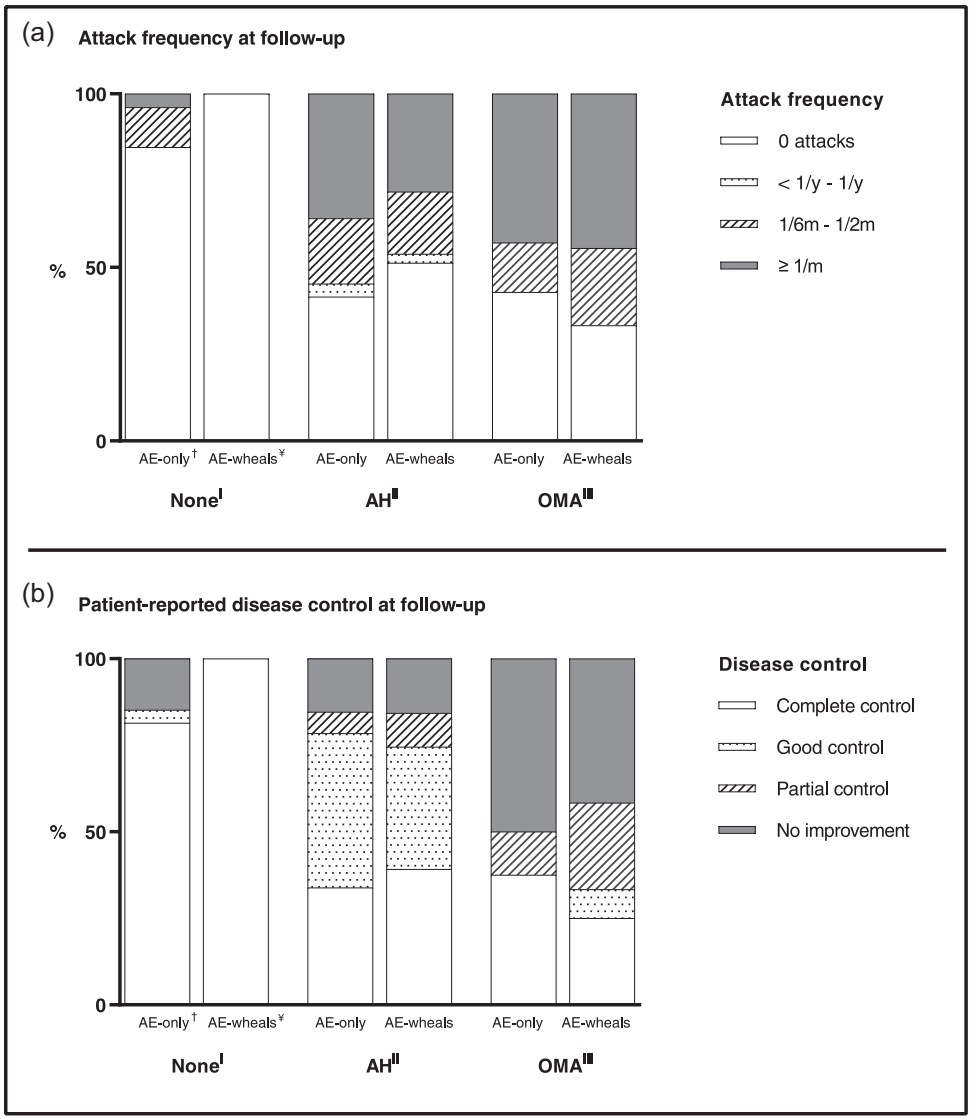

FIGURE 1 (a) Attack frequency at follow-up per AE subgroup and maximum prescribed prophylactic therapy. Subgroups are displayed as bars, grouped per prophylactic treatment strategy. The shade represents the attack frequency category. $N = 137$ as for 99 patients information on attack frequency was not available. †Angioedema patients without wheals; ¥Angioedema patients with wheals; I none ($n = 29$); II antihistamines ($n = 92$); III omalizumab ($n = 16$). (b) Patient-reported disease control at follow-up per AE subgroup and maximum prescribed prophylactic therapy. Subgroups are displayed as bars, grouped per prophylactic treatment strategy. The shade represents the patient-reported disease control category. $N = 166$ as for 70 patients information on disease control was not available. †Angioedema patients without wheals; ¥Angioedema patients with wheals; I none ($n = 30$); II antihistamines ($n = 116$); III omalizumab ($n = 20$).

Acute attack treatment use was largely reduced after the initiation of prophylactic treatment

To obtain an indication of the severity of attacks, acute attack treatment was analysed per prophylactic treatment strategy: no prophylactic treatment, antihistamine monotherapy and omalizumab. Acute attack treatment use and emergency intervention was decreased during follow-up compared to at first presentation ($n = 59$, 42% vs. $n = 182$, 80%). At follow-up, after maximum prophylactic treatment prescription, use of urgent care was seen in 10% ($n = 3$), 5% ($n = 5$) and 25% ($n = 5$) of patients with no prophylactic treatment, antihistamine monotherapy or omalizumab respectively (Supporting Information: Figure S2, Table S1).

No difference in response to prophylactic treatment between AE-only and AE-wheals patients

To identify differences between AE-only and AE-wheals patients, prophylactic treatment strategies and their treatment response upon these strategies were compared between the two groups. At first presentation, significantly more AE-wheals patients ($n = 52$, 54%) used prophylactic treatment compared to AE-only patients ($n = 40$, 29%, $p < 0.001$). Similarly, during follow-up prophylactic treatment was prescribed more often (90%) to AE-wheals patients compared to AE-only patients (61%, $p < 0.001$) (Table 2). This corresponds to a significantly higher attack frequency (at least 1 per month) in AE-wheals patients ($n = 69$, 71%) compared to AE-only patients ($n = 70$, 50%) at first visit, suggesting this difference is related to disease severity, but not disease entity.

Despite the higher use of prophylactic treatment in AE-wheals patients, at follow-up no difference in attack frequencies, patient-reported disease control and acute attack treatment were found compared to AE-wheals patients. Hence, therapeutic response to antihistamines or add-on treatment with omalizumab between AE-only and AE-wheals patients during follow-up did not differ.

DISCUSSION

To our knowledge, this is the first study focusing specifically on the disease severity profile related to prophylactic treatment response in a large population of idiopathic AE patients and additionally differentiating between AE patients with and without concomitant subordinary wheals. The percentages of maximum prescribed prophylactic treatment during follow-up were distributed as (1) 27% with no prophylactic treatment; (2) 59% antihistamine monotherapy and (3) 14% of patients with add-on treatment, of which 9% was with omalizumab. Well-controlled disease was seen in the majority of patients with no prophylactic treatment or antihistamine monotherapy (86% and 68%, respectively) showing no attacks or low attack frequency only. Of patients with, specifically, a fourfold dose of antihistamines, 64% showed no or minimal symptoms (complete or good response). A relatively small, but substantial proportion required add-on treatment with omalizumab (9%), of which more than half of patients were well-controlled with no attacks or low attack frequency; but still 44% suffered from a high attack frequency during follow-up. Notably, we found no significant difference in treatment response to antihistamines or omalizumab between patients with AE with and without wheals.

To obtain a more comprehensive impression of disease severity, we analysed additional outcomes such as patient-reported disease control and acute attack treatment. Resembling attack frequency, the majority of patients without prophylactic treatment or antihistamine monotherapy reported no or minimal symptoms (complete or good control response) (87% and 77%, respectively). Furthermore, we found a decrease in the use of acute attack treatment and intervention after maximum prophylactic treatment prescription at follow-up, suggesting not only lower attack frequency, but also milder attacks due to maximum prophylactic treatment for each prophylactic treatment strategy. No other studies have looked into acute attack treatment in relation to prophylactic treatment.

No prophylactic treatment was used in a substantial part of our population (27%), of which the majority showed no attack during follow-up, illustrating that the natural course of the disease can be mild and self-limiting. This was also supported by our finding that 81% of this group did not use any attack treatment. In our literature review, we did not find any data allowing comparison of the disease in AE patients without prophylactic treatment with other populations.

Antihistamine monotherapy, used by 59% of our population, resulted in complete response and low attack frequency in 46% and 22%, respectively. In preceding studies, the effect of antihistamines in AE patients was analysed with regard to the current classification of AAE, which defines patients as IH-AAE or InH-AAE based on the response to antihistamine therapy.[2,3] The effect of antihistamines on AE was previously studied mainly in AE patients without wheals.[10–13] These studies found similar complete response rates at follow-up after antihistamine monotherapy (in variable dosage) ranging from 56% to 72%[10,11] and improvement of attack frequency in 86%–91%.[12,13] Notably, in our study, the presence of wheals did not influence antihistamine therapy outcome, resulting in an antihistamine response rate of 68% in AE patients with and without wheals that is comparable with the response rates in AE patients without wheals as shown in these previous studies.

Nine percent of our patients received omalizumab, which led to complete response in 38% and low attack frequency in 18% of patients, which was comparable for AE patients with and without wheals. Previous studies investigated the effect of omalizumab for CSU patients and showed well-controlled disease in 52%–63%[14,15] and complete response in 34%–40% of CSU patients,[15] which are higher rates compared to our results. Data regarding

therapeutic response to omalizumab in AE patients without wheals is limited to 10 case reports with a total of 30 patients. These reports showed response in all cases with complete response in 57% ($n = 17$) and partial or good response in 43% ($n = 13$) of patients.[8,9] However, due to the sensitivity of case reports to publication bias, effectiveness of omalizumab in AE patients in current literature is probably overestimated. Therefore, we expect real-world effectiveness of omalizumab for patients with idiopathic AE to be lower and correspond more to the percentage found in our study, which needs to be proven in prospective studies.

In conformance with CSU guidelines,[2,3] in daily practice, patients with idiopathic AE are treated with omalizumab in cases of insufficient response to a fourfold dose of antihistamines. Given the data of this study, we can extrapolate that approximately 92% of the AE population is well-controlled without prophylactic treatment, antihistamines or add-on treatment and that 8% remain difficult to treat due to unresponsiveness to these therapeutic options and the absence of other available treatment options. A notable finding in our study was that the response to antihistamines and omalizumab was irrespective of the presence of wheals. This implies that the presence of wheals is not indicative of an underlying histamine-mediated mechanism and that other common pathophysiologic mechanisms, such as bradykinin, might play a role. This concept was recently suggested in a study demonstrating elevated plasma Csk-homologous kinase levels in CSU patients compared to healthy controls.[16] This finding, however, could not be related to clinical response to antihistamines. Nonetheless, bradykinin might contribute to the pathophysiologic mechanism of AE and wheals, since previous research has shown that the bradykinin-forming contact system is involved in mast cell-mediated reactions and processes.[17] This may explain limited treatment response for both symptoms in patients with a certain phenotype. Further research is needed to unravel the specific pathophysiologic mechanism in patients suffering from AE and/or wheals not responding to antihistamines or anti-IgE therapy. Such research will enable better treatment strategies to be explored.

Although we found no difference in treatment response between AE patients with and without wheals, AE patients without wheals were older (48 vs. 43 years) and reported more often a swelling of the tongue compared to AE patients with wheals (50% vs. 33%). This is also described in a recent prospective study, which found significantly more frequent tongue swellings in AE patients without wheals compared to AE patients with wheals (59% vs. 29%).[18] Tongue swelling is frequently seen in patients with IH-AAE, C1-INH deficiency and ACEI-AE.[5] However, it is questionable whether this specific symptom can be explained by a specific pathophysiologic mechanism (e.g., histaminergic or bradykinin-mediated AE) in patients with or without wheals. Yet, we did not find any differences in response to antihistamines based on attack frequency and patient-reported disease control between patients with and without tongue swelling.

An important advantage of this study is the large cohort of idiopathic AE patients with a defined minimum follow-up period of 90 days. However, several limitations need to be mentioned: its retrospective design, resulting in missing values and variations in follow-up duration and the lack of validated patient outcome scores AE activity score (AAS) and urticaria control test (UCT), which were only available in a proportion of patients from recent years, resulting in more subjective outcomes.

In conclusion, we describe an idiopathic AE population profile showing a majority of patients with well-controlled disease requiring no prophylactic treatment or antihistamine monotherapy only. A minority requires add-on treatment with insufficient response in a substantial proportion. AE severity profile and treatment response were independent from presence of wheals.

AUTHOR CONTRIBUTIONS

Study conceptualisation and methodology: Heike Röckmann, Mehran Alizadeh Aghdam and Reineke Soegiharto. *Data collection*: Reineke Soegiharto. *Data analysis*: Reineke Soegiharto. *Interpretation of results*: Andre C. Knulst, Heike Röckmann, Mehran Alizadeh Aghdam and Reineke Soegiharto. *Writing manuscript*: Andre C. Knulst, Heike Röckmann, Mehran Alizadeh Aghdam and Reineke Soegiharto. *Supervision*: Andre C. Knulst and Heike Röckmann.

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CONFLICTS OF INTEREST

Andre C. Knulst received a health care innovation grant from Novartis and is a member of the national and international advisory board of Novartis for CSU. Heike Röckmann is a member of the national advisory board of Novartis for CSU. Mehran Alizadeh Aghdam received a speakers fee from Novartis. Reineke Soegiharto declares no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The local medical ethics committee declared that WMO approval was not required (protocol number 20-327).

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REFERENCES

1. Kaplan AP, Greaves MW. Angioedema. J Am Acad Dermatol. 2005;53(3):373–88. https://doi.org/10.1016/j.jaad.2004.09.032
2. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2021 revision and update. Allergy. 2022;77(7):1961–90. https://doi.org/10.1111/all.15214
3. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734–66. https://doi.org/10.1111/all.15090
4. Sussman G, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: analyses from ASSURE-CSU. Allergy. 2018;73(8):1724–34. https://doi.org/10.1111/all.13430
5. Maurer M, Magerl M. Differences and similarities in the mechanisms and clinical expression of Bradykinin-mediated vs. mast cell–mediated angioedema. Clin Rev Allergy Immunol. 2021;61(1):40–9. https://doi.org/10.1007/s12016-021-08841-w
6. Marzano AV, Maronese CA, Genovese G, Ferrucci S, Moltrasio C, Asero R, et al. Urticarial vasculitis: clinical and laboratory findings with a particular emphasis on differential diagnosis. J Allergy Clin Immunol. 2022;149(4):1137–49. https://doi.org/10.1016/j.jaci.2022.02.007
7. Belbézier A, Bocquet A, Bouillet L. Idiopathic angioedema: current challenges. J Asthma Allergy. 2020;13:137–44. https://doi.org/10.2147/JAA.S205709
8. van den Elzen M, Go MFCL, Knulst AC, Blankestijn MA, van Os-Medendorp H, Otten HG. Efficacy of treatment of non-hereditary angioedema. Clin Rev Allergy Immunol. 2018;54(3):412–31. https://doi.org/10.1007/s12016-016-8585-0
9. Bucher MC, Petkovic T, Helbling A, Steiner UC. Idiopathic non-histaminergic acquired angioedema: a case series and discussion of published clinical trials. Clin Transl Allergy. 2017;7(1):27. https://doi.org/10.1186/s13601-017-0164-9
10. Mansi M, Zanichelli A, Coerezza A, Suffritti C, Wu MA, Vacchini R, et al. Presentation, diagnosis and treatment of angioedema without wheals: a retrospective analysis of a cohort of 1058 patients. J Intern Med. 2015;277(5):585–93. https://doi.org/10.1111/joim.12304
11. Pall AH, Lomholt AF, Buchwald C, von Bygum A, Rasmussen ER. Clinical features and disease course of primary angioedema patients in a tertiary care hospital. J Asthma Allergy. 2020;13:225–36. https://doi.org/10.2147/JAA.S245161
12. Rosenberg DL, Mathur SK, Viswanathan RK. Characterization of idiopathic angioedema in a university-based allergy/immunology practice. Ann Allergy Asthma Immunol. 2019;123(4):403–4. https://doi.org/10.1016/j.anai.2019.07.023
13. Zingale LC, Beltrami L, Zanichelli A, Maggioni L, Pappalardo E, Cicardi B, et al. Angioedema without urticaria: a large clinical survey. Can Med Assoc J. 2006;175(9):1065–70. https://doi.org/10.1503/cmaj.060535
14. Vadasz Z, Tal Y, Rotem M, Shichter-Confino V, Mahlab-Guri K, Graif Y, et al. Omalizumab for severe chronic spontaneous urticaria: real-life experiences of 280 patients. J Allergy Clin Immunol Pract. 2017;5(6):1743–5. https://doi.org/10.1016/j.jaip.2017.08.035
15. Giménez-Arnau AM. Omalizumab for treating chronic spontaneous urticaria: an expert review on efficacy and safety. Expert Opin Biol Ther. 2017;17(3):375–85. https://doi.org/10.1080/14712598.2017.1285903
16. Hofman ZLM, den Elzen MT, Kuijpers J, Maat S, Hack CE, Knulst AC, et al. Evidence for bradykinin release in chronic spontaneous urticaria. Clin Exp Allergy. 2020;50(3):343–51. https://doi.org/10.1111/cea.13558
17. Sala-Cunill A, Björkqvist J, Senter R, Guilarte M, Cardona V, Labrador M, et al. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. J Allergy Clin Immunol. 2015;135(4):1031–43. https://doi.org/10.1016/j.jaci.2014.07.057
18. Sabaté-Brescó M, Rodriguez-Garijo N, Azofra J, Baeza ML, Donado CD, Gaig P, et al. A comparative study of sex distribution, autoimmunity, blood, and inflammatory parameters in chronic spontaneous urticaria with angioedema and chronic histaminergic angioedema. J Allergy Clin Immunol Pract. 2021;9(6):2284–92. https://doi.org/10.1016/j.jaip.2021.03.038

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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