Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

EDITORIAL

Angioedema is not just 'deep urticaria' but an entity of its own

DOI:10.1111/all.12362

Urticaria and angioedema are among the most common diseases seen by dermatologists. Although these disorders frequently occur together and are addressed jointly in guidelines (1), they are by no means synonymous. In fact, they can be distinguished quite easily by their gross appearance, speed of onset, duration, anatomic location, and severity of symptoms. Most importantly, their pathophysiology and consequently their treatment may be different. Urticaria is usually mediated by mast cells with histamine the main protagonist and responds well to treatment with corticosteroids and/or antihistamines. In contrast, bradykinin is of major functional significance in many forms of angioedema (2). This explains why angiotensin-converting enzyme (ACE)-inhibitor-induced life-threatening angioedema of the upper respiratory tract frequently does not respond to standard allergy treatment with antihistamines, corticosteroids, and epinephrine, but requires drugs that block this mediator (3). These and several other new observations made necessary the drafting of a consensus report by an expert group for the purpose of classifying, diagnosing, and treating angioedema that appears in this issue of *Allergy* (4). The high number of articles published in this as well as in many other journals in the past few years mirrors the substantial progress in the field.

Algorithms for diagnosing patients with recurrent hives or angioedema led to the realization that addressing urticaria and angioedema may lead the investigator in entirely different directions (5). While several unmet needs in regard to chronic urticaria are difficult to fulfill (6), decisive breakthroughs have been achieved in the last few years in respect to various forms of angioedema. A specific quality-of-life questionnaire for chronic angioedema (7) and an angioedema activity score (8) have been developed. An international consensus on (ICON) hereditary and acquired angioedema led to agreement on the partly diverse viewpoints expressed by European and American experts (9). The advances made in characterizing three very different forms of angioedema, namely hereditary angioedema (HAE), the – meanwhile historical term – HAE type III, and ACE-inhibitor-induced angioedema, were of groundbreaking significance.

The greatest impetus for the progress made in the last few years was provided by the Orphan Drug Act (ODA) in the USA in 1983 and Regulation (EC) No. 141/2000 of the European Union. Their purpose is to encourage pharmaceutical companies to develop drugs for diseases that have only a small market. Until a few years ago, only attenuated androgens, antifibrinolytic agents, and fresh-frozen plasma were available in most countries for the treatment of HAE, a disease with a worldwide prevalence of about 1/50 000 persons (10). The effects of these agents were unreliable, and their side effect profile was problematic. These statutory regulations stimulated a large number of clinical studies on substitution of factor C1-INH, as well as the development of new drugs focusing on various target points. Some of these drugs are now available in the market while others will be launched shortly (11).

The wide range of therapies with conventionally derived and recombinant C1-INH as well as receptor blockers for kallikrein and bradykinin also led to the need for evidence-based recommendations in regard of the therapeutic management (12). The goal of treatment is aimed at avoiding mortality and reducing morbidity. This required a variety of guidelines on gynecological and obstetric management of female patients (13) as well as a consensus on therapeutic strategies for children and adolescents (14). Until a few years ago, androgens – which are problematic when used for maintenance therapy – were widely employed for HAE even in children and women, while tranexamic acid, a substance with unreliable effects, was used to treat acute attacks. In fact, many angioedema attacks were not treated with the substitution product C1-INH even in countries where it was available (15). However, the treatment options have changed dramatically in the last few years. This is a blessing for patients because HAE is not only associated with serious morbidity, but also with high mortality due to laryngeal attacks, if untreated (16). Failure to treat attacks is in part attributable to the problem that the onset of swelling could not be predicted because reliable laboratory markers for acute attacks were not available. The diagnostic value of the prothrombin fragment F1 + 2 and D-dimer levels has been proven only recently (17).

Mutation analyses in Brazil (18), Denmark (19), China (20), and other countries have shown the diversity of mutations in the C1-INH gene and their impact on C1-INH levels, but there seems to be little correlation between the type of mutation and severity of symptoms. Surprisingly, the observation that the sense of smell is impaired in many patients with HAE was first reported in 2011. The severity of smell impairment appears to correlate with complement levels (21). Predictors of perioperative attacks are also not available (22). However, depending on the type of surgery (abdominal, ENT, or gynecological procedures), the maximum potential risk to develop an angioedema is around 30% (22). Therefore, current treatment guidelines suggest that one should consider short-term prophylaxis with C1-INH for all patients with HAE undergoing surgery (23) or, if C1-INH is not available, with attenuated androgens or antifibrinolytic agents. However, C1-INH is significantly superior to orally administered

drugs in reducing postprocedural edema (24). In off-label use, the bradykinin B2 receptor antagonist icatibant also proved to be safe, free of side effects, and feasible for this indication (25). In patients with frequent or severe spontaneous HAE attacks, according to the international recommendations (12), permanent prophylaxis with the missing C1-INH should be considered. Long-term prophylaxis reduces the frequency and severity of disease and improves quality of life (26). Intravenous human plasma-derived C1-INH concentrates have been used for this purpose since 1989 (27). All, that are the conventional products (27), a nanofiltered pdC1-INH (28), as well as a recombinant product (29) proved to be safe and effective. The response can be quite variable: some patients experience no change in their frequency of attacks while others are almost free of attacks. The pressing question of who would benefit from the individualized treatment approach was addressed in a recent publication (30).

In the last few years, the greatest advances have been made in the treatment of acute attacks, also known as on-demand treatment, through numerous studies focusing on recently developed drugs. In a study performed in Germany from 1976 to 2007 on the treatment of 2014 episodes of angioedema involving the skin and soft tissues, the administration of a single dose of 500 IU of pdC1-INH, independent of body weight, usually proved sufficient (31). But marketing authorization studies have demonstrated the necessity of using 20 IU/kg for the treatment of acute attacks (32). In addition, infusions of plasma-derived and recombinant C1-INH concentrates (28, 32, 33) have been shown to be effective for the treatment of acute HAE attacks involving any organ system. In controlled (34) as well as open studies (35), subcutaneous administration of the bradykinin B2 receptor antagonist icatibant was found to be safe and effective. This substance is a convenient alternative to intravenous infusions (36). Self-treatment as an alternative to treatment by healthcare professionals permits immediate treatment of acute attacks and is associated with more rapid response and earlier resolution of the swelling (37). Treatment with the plasma kallikrein inhibitor ecallantide is also effective; relapses were observed in only a small number of patients, and there was little evidence of a rebound effect (38).

In acquired angioedema with C1 inhibitor deficiency, caused by autoantibodies neutralizing C1-INH-binding epitopes or by the consumption of C1-INH in lymphoproliferative disease, the attacks may be treated with C1-INH replacement therapy (4). However, some patients may be resistant to this treatment because of extremely rapid catabolism of C1-INH. The efficacy of on-demand subcutaneous administration of icatibant has been reported in a small series of such patients, including those resistant to plasma-derived C1-INH (4). In one case series comprising 48 moderate-to-severe attacks, complete resolution of symptoms was achieved in 47 cases after a single injection of icatibant; only one facial attack required a second injection (39).

Hereditary angioedema with normal C1-INH function, first described in 2000 (40), has been a controversial term from the very start (41). Patients with this condition are now subdivided into two groups: one with a mutation in the F12 gene and a second group with an unknown genetic defect (4). This mutation in the F12 gene was recently reported in patients from an Arabian family (42), from Spain (43), and from France (44). Patients from these countries with unknown defects have also been reported on. Both groups do not respond to antihistamines and steroids (45), but do respond to C1-INH replacement, ecallantide, progesterone, danazol, and tranexamic acid (4). This information is derived from studies on a very limited number of patients.

Because ACE inhibitors (ACEI) are so widely used antihypertensive agents, it is not surprising that ACEI-induced acquired angioedema (ACEI-AAE) accounts for the majority of bradykinin-mediated angioedema. Analysis of large cohorts of hypertensive patients suggests that angioedema occurs in less than 0.5% of patients taking ACEI; its prevalence is 3- to 4.5-fold higher in black persons than in Caucasians (4). Transplanted patients are subject to a high risk of ACEI-AAE, possibly because of the effects of immunosuppressants on the activity of circulating dipeptidyl peptidase IV (46). In addition to the immediate discontinuation of ACEI after the first episode, a variety of medications approved for the treatment of HAE have been used to treat this condition (4). In an uncontrolled study on 20 patients with ACEI-AAE, icatibant led to rapid and complete resolution of symptoms (3).

Angioedema should be regarded as a distinct and separate entity. It may occur in various forms and can be identified by specific criteria (4). The absence of studies on angioedema other than C1-INH-deficient or classic HAE has hindered the development of an evidence-based therapeutic strategy. Algorithms have been created for diagnostic investigation of patients with angioedema with (47) and without urticaria (5). Various therapeutic agents have been effective in uncontrolled studies, but are only partly approved for specific indications or are currently in the final stages of development. Controlled studies for appropriate treatment for angioedema-related mortality and disability should be performed in the future (4). Much has been achieved, but even more needs to be done.

Conflict of interest

The author has served as a speaker for and received funding for travel and meeting from CSL Behring, Shire, and Viropharma; and participated in studies with Shire.

W. Aberer
Department of Dermatology, Medical University of Graz, Graz, Austria
E-mail: werner.aberer@medunigraz.at

References

1. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW et al. The EAACI/GA^{2}LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014, doi: 10.1111/all.12313.

2. Maurer M, Bader M, Bas M, Bossi F, Cicardi M, Cugno M et al. New topics in bradykinin research. *Allergy* 2011;**66**:1397–1406.
3. Bas M, Greve J, Stelter K, Bier H, Stark T, Hoffmann TK et al. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. *Ann Emerg Med* 2010;**56**:278–282.
4. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K et al. Classification, diagnosis and approach to treatment of angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy* 2014;**69**:602–616.
5. Zingale LC, Beltrami L, Zanichelli A, Maggioni L, Pappalardo E, Cicardi B et al. Angioedema without urticaria: a large clinical survey. *CMAJ* 2006;**175**:1065–1070.
6. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy* 2011;**66**:317–330.
7. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy* 2012;**67**:1289–1298.
8. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K et al. Development, validation, and initial results of the Angioedema Activity Score. *Allergy* 2013;**68**:1185–1192.
9. Lang DM, Aberer W, Bernstein JA, Chng HH, Grumach AS, Hide M et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol* 2012;**109**:395–402.
10. Longhurst H, Cicardi M. Hereditary angioedema. *Lancet* 2012;**379**:474–481.
11. Aberer W. Hereditary angioedema treatment options: the availability of new therapies. *Ann Med* 2012;**44**:523–529.
12. Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012;**67**:147–157.
13. Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol* 2012;**129**:308–320.
14. Wahn V, Aberer W, Eberl W, Fasshauer M, Kuhne T, Kurnik K et al. Hereditary angioedema (HAE) in children and adolescents–a consensus on therapeutic strategies. *Eur J Pediatr* 2012;**171**:1339–1348.
15. Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy* 2011;**66**:192–196.
16. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 2012;**130**:692–697.
17. Cugno M, Zanichelli A, Bellatorre AG, Griffini S, Cicardi M. Plasma biomarkers of acute attacks in patients with angioedema due to C1-inhibitor deficiency. *Allergy* 2009;**64**:254–257.
18. Ferraro MF, Moreno AS, Castelli EC, Donadi EA, Palma MS, Arcuri HA et al. A single nucleotide deletion at the C1 inhibitor gene as the cause of hereditary angioedema: insights from a Brazilian family. *Allergy* 2011;**66**:1384–1390.
19. Bygum A, Fagerberg CR, Ponard D, Monnier N, Lunardi J, Drouet C. Mutational spectrum and phenotypes in Danish families with hereditary angioedema because of C1 inhibitor deficiency. *Allergy* 2011;**66**:76–84.
20. Xu YY, Zhi YX, Yin J, Wang LL, Wen LP, Gu JQ et al. Mutational spectrum and genophenotype correlation in Chinese families with hereditary angioedema. *Allergy* 2012;**67**:1430–1436.
21. Perricone C, Agmon-Levin N, Shoenfeld N, de Carolis C, Guarino MD, Gigliucci G et al. Evidence of impaired sense of smell in hereditary angioedema. *Allergy* 2011;**66**:149–154.
22. Aygoren-Pursun E, Martinez Saguer I, Kreuz W, Klingebiel T, Schwabe D. Risk of angioedema following invasive or surgical procedures in HAE type I and II - the natural history. *Allergy* 2013;**68**:1034–1039.
23. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;**6**:24.
24. Farkas H, Zotter Z, Csuka D, Szabo E, Nebenfuhrer Z, Temesszentandrasi G et al. Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor–a long-term survey. *Allergy* 2012;**67**:1586–1593.
25. Marques L, Domingo D, Maravall FJ, Clotet J. Short-term prophylactic treatment of hereditary angioedema with icatibant. *Allergy* 2010;**65**:137–138.
26. Longhurst HJ, Farkas H, Craig T, Aygoren-Pursun E, Bethune C, Bjorkander J et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol* 2010;**6**:22.
27. Bork K, Witzke G. Long-term prophylaxis with C1-inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 1989;**83**:677–682.
28. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;**363**:513–522.
29. Reshef A, Moldovan D, Obtulowicz K, Leibovich I, Mihaly E, Visscher S et al. Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: a pilot study. *Allergy* 2013;**68**:118–124.
30. Porebski G, Reshef A, Moldovan D. The prophylaxis of hereditary angioedema attacks with recombinant human C1 inhibitor: who will take advantage of the individualized treatment approach? *Allergy* 2013;**68**:1207–1209.
31. Bork K, Staubach P, Hardt J. Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema. *Allergy* 2008;**63**:751–757.
32. Craig TJ, Bewtra AK, Bahna SL, Hurewitz D, Schneider LC, Levy RJ et al. C1 esterase inhibitor concentrate in 1085 Hereditary Angioedema attacks–final results of the I.M.P.A.C.T.2 study. *Allergy* 2011;**66**:1604–1611.
33. Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010;**126**:821–827.
34. Cicardi M, Banerji A, Bracho F, Malbran A, Rosenkranz B, Riedl M et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010;**363**:532–541.
35. Bas M, Greve J, Hoffmann TK, Reshef A, Aberer W, Maurer M et al. Repeat treatment with icatibant for multiple hereditary angioedema attacks: FAST-2 open-label study. *Allergy* 2013;**68**:1452–1459.
36. Aberer W, Maurer M, Reshef A, Longhurst H, Kivity S, Bygum A et al. Open-label, multicenter study of self-administered icatibant for attacks of hereditary angioedema. *Allergy* 2014;**69**:305–314.
37. Maurer M, Aberer W, Bouillet L, Caballero T, Fabien V, Kanny G et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. *PLoS ONE* 2013;**8**:e53773.
38. Bernstein JA, Shea EP, Koester J, Iarrobino R, Pullman WE. Assessment of rebound and relapse following ecallantide treatment for acute attacks of hereditary angioedema. *Allergy* 2012;**67**:1173–1180.
39. Zanichelli A, Bova M, Coerezza A, Petraroli A, Triggiani M, Cicardi M. Icatibant treatment for acquired C1-inhibitor deficiency: a real-world observational study. *Allergy* 2012;**67**:1074–1077.

40. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000;**356**:213–217.
41. Kranke B, Salmhofer W, Aberer W. Hereditary angioedema and normal C1-inhibitor activity in women. *Lancet* 2000;**356**:1440–1441.
42. Baeza ML, Rodriguez-Marco A, Prieto A, Rodriguez-Sainz C, Zubeldia JM, Rubio M. Factor XII gene missense mutation Thr328Lys in an Arab family with hereditary angioedema type III. *Allergy* 2011;**66**:981–982.
43. Prieto A, Tornero P, Rubio M, Fernandez-Cruz E, Rodriguez-Sainz C. Missense mutation Thr309Lys in the coagulation factor XII gene in a Spanish family with hereditary angioedema type III. *Allergy* 2009;**64**:284–286.
44. Vitrat-Hincky V, Gompel A, Dumestre-Perard C, Boccon-Gibod I, Drouet C, Cesbron JY et al. Type III hereditary angio-oedema: clinical and biological features in a French cohort. *Allergy* 2010;**65**:1331–1336.
45. Bork K. Diagnosis and treatment of hereditary angioedema with normal C1 inhibitor. *Allergy Asthma Clin Immunol* 2010;**6**:15.
46. Byrd JB, Woodard-Grice A, Stone E, Lucisano A, Schaefer H, Yu C et al. Association of angiotensin-converting enzyme inhibitor-associated angioedema with transplant and immunosuppressant use. *Allergy* 2010;**65**:1381–1387.
47. Maurer M, Magerl M, Metz M, Siebenhaar F, Weller K, Krause K. Practical algorithm for diagnosing patients with recurrent wheals or angioedema. *Allergy* 2013;**68**:816–819.