Psychology and hereditary angioedema: A systematic review

Livia Savarese, Ph.D.,[1] Ilaria Mormile, M.D.,[2] Maria Bova, M.D. Ph.D.,[2] Angelica Petraroli, M.D.,[2] Assunta Maiello, M.Psy.,[1] Giuseppe Spadaro, M.D.,[2] and Maria Francesca Freda, M.Psy., Ph.D.[1]

ABSTRACT

Background: *Hereditary angioedema (HAE) is caused by mutations in the C1 inhibitor (C1-INH) gene Serpin Family G Member 1(*SERPING1*), which results in either the decreased synthesis of normal C1-INH (C1-INH–HAE type I) or expression of unfunctional C1-INH (C1-INH–HAE type II). In recent studies, emotional stress was reported by patients as the most common trigger factor for C1-INH–HAE attacks. Moreover, patients reported considerable distress over the significant variability and uncertainty with which the disease manifests, in addition to the impact of physical symptoms on their overall quality of life.*

Objective: *We did a systematic review of the literature to shed light on the advancements made in the study of how stress and psychological processes impact C1-INH–HAE.*

Methods: *All of the articles on C1-INH–HAE were analyzed up to December 2019. Both medical data bases and psychological data bases were examined. The keywords (KWs) used for searching the medical and psychological data bases were the following: "hereditary angioedema," "psychology," "stress," "anxiety," and "depression."*

Results: *Of a total of 2549 articles on C1-INH–HAE, 113 articles were retrieved from the literature search by using the related KWs. Twenty-one of these articles were retrieved, examined, and classified.*

Conclusion: *Although the literature confirmed that stress may induce various physical diseases, it also warned against making simplistic statements about its incidence that did not take into account the complexity and multicausality of factors that contribute to C1-INH–HAE expression.*

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Hereditary angioedema (HAE) is a rare and potentially life-threatening disorder characterized by an increase in blood vessel permeability,[1] which results in recurrent episodes of swelling within the cutaneous and subcutaneous tissue. Mutations in the C1 inhibitor (C1-INH) gene (*SERPING1*) result in the decreased synthesis of normal C1-INH (C1-INH HAE type I) or the expression of unfunctional C1-INH (C1-INH HAE type II).[2,3]

C1-INH–HAE attacks are typified by subcutaneous edema in the skin, gastrointestinal tract, and upper respiratory tract. Suffocation can result when this swelling occurs in the mucosa of the upper airways and the body becomes deprived of oxygen.[4] Indeed, the leading cause of death among patients who die of C1-INH–HAE is asphyxiation,[5,6] for which patients maintain a low but permanent risk.[6] Given the hereditary nature of the disease and the likelihood that their ancestors had succumbed to a similar fate (*i.e.*, asphyxiation induced by laryngeal swelling), patients may live in constant fear of the attacks getting worse and of not being able to breathe.[5,7,8]

In a survey of 63 patients with C1-INH–HAE,[9] the authors identified patients' greatest fears as the following: fear of sudden airway closure (85%), intolerable pain (65%), and transmission of the disease to their children (55%).[9] Because patients, in addition, may have spasms, colic pain, vomiting, diarrhea, and disfiguration, they may also experience difficulties in carrying out activities associated with daily living.[10] Indeed, estimates state that patients with C1-INH–HAE lose between 20 and 100 days of social activities each year.[9,11] C1-INH–HAE not only causes substantial short-term disability associated with its attacks, but it may also cause patients to live in persistent anxiety between episodes. The disease's unpredictable nature could directly impact patients' choices in everyday life. It may cause individuals to avoid traveling, specific hobbies, or social opportunities, or it may cause them to experience anxiety about having children or may cause other social and/or relationship impairment.[7]

Factors such as infections, emotional stress, physical exertion, trauma, invasive medical procedures, menstruation, and treatment with certain medications (*i.e.*, Angiotensin-converting Enzyme (ACE) Inhibitors or estrogen-containing medications) can trigger C1-INH–HAE attacks.[1] In a recent study, Zotter *et al.*[12] found

From the [1]Department of Humanities, University Federico II, Naples, Italy, and [2]Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research, University of Naples Federico II, World Allergy Organization Center of Excellence, Naples, Italy

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Address correspondence to Maria Bova, M.D., Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research, University of Naples Federico II, WAO Center of Excellence, Naples, Italy

E-mail address: bovamaria@virgilio.it

that emotional stress is the most common trigger factor of attacks reported by patients. This stress could lead to a vicious cycle in which anxiety over continuing attacks could trigger further episodes.[13,14] Another notable feature of C1-INH–HAE is the substantial variability in attack frequency and severity observed among patients affected by the same C1-INH–HAE type and even in the same patient during different stages of life. Indeed, some patients have frequent, life-threatening attacks that necessitate long-term prophylaxis (LTP), whereas others experience a mild disease course that is well controlled by on-demand therapy (ODT).

The factors that influence this heterogeneous clinical expression represent one of the oldest mysteries of the disease. It is generally accepted that there is little correlation between *SERPING1* mutations and disease phenotype[15] and that neither C4 nor C1-INH levels reflect the clinical course of the disease.[16] Collectively, these elements could complicate disease management, which thus affects the health-related quality of life (HRQoL) for patients with C1-INH–HAE. This article aimed to provide clinicians with an accurate picture of the most current knowledge that surrounds the role that emotions, stress, and psychological factors play in the experience of patients with C1-INH–HAE.

METHODS

Protocol

For this systematic review (SR), we referred to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Metanalyses) guidelines.[17] The research procedures were established *a priori* in an operational protocol in which research strategies, inclusion and exclusion criteria, and data collection strategies were made explicit.

Eligibility Criteria

Included in the review were all articles from December 2019 and earlier, written in English, and published in peer-reviewed, international journals, and in the leading online data bases, and which dealt with the psychological aspects of C1-INH–HAE.

Research Method

All of the articles on C1-INH–HAE were analyzed up to December 2019 without setting limits around the commencement year of the SR. To identify all the studies that included psychological dimensions related to the illness experience, both medical data bases (PubMed and Embase (Excerpta Medica dataBASE, Elsevier, Amsterdam)) and a psychological data base (PsycInfo (American Psychological Association, USA)) were examined. The keywords (KWs) used for searching PubMed and Embase were the following: "hereditary angioedema," "psychology," "stress," "anxiety," and "depression." These KWs were selected from a preliminary bibliography[12,18] as psychological processes relevant to the C1-INH–HAE illness experience. Only the KWs that returned results from the aforementioned data bases are shown, whereas any KWs used without returning results (*e.g.,* "psychological correlates") were not reported. The KWs search and the analysis were performed on the whole manuscript file.

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RESULTS

Of a total of 2549 articles on C1-INH–HAE, 113 articles were retrieved from the literature search by using the related KWs (Figure 1). Articles that mentioned stress and psychological factors, among other triggers, without an *ad hoc* assessment by psychometric or qualitative measures, were excluded from the SR. Twenty-one of these articles were retrieved, examined, and classified according to two criteria: direct studies (n = 17) that explicitly examined the role of psychological stress and emotional processes, and indirect studies (n = 4) aimed at evaluating other aspects related to the C1-INH–HAE experience but that were consistent with the SR criteria. All the examined articles refer to the publication period between 1989 and 2019 (Fig. 1).

As shown in Supplemental Table 1, 17 studies explicitly examined psychological aspects of C1-INH–HAE through observational case-control studies, for which a mixed-method research design and literature review were preferred.[7,10,13,14,19–25,27–32] There were no randomized controlled trials. These studies involved participants who belonged to three age groups: adult patients and caregivers, children, and adolescents.[10,19] All the subjects were selected through purposive sampling from specialist care centers that treat patients affected by C1-INH–HAE. Psychological aspects explored by the literature mainly focused on anxiety and depression disorders, stress, emotion regulation, and quality of life (QoL). These studies primarily relied on the use of psychometric tests,[10,19–24] qualitative surveys,[7,25–28] and reviews.[14,29,30]

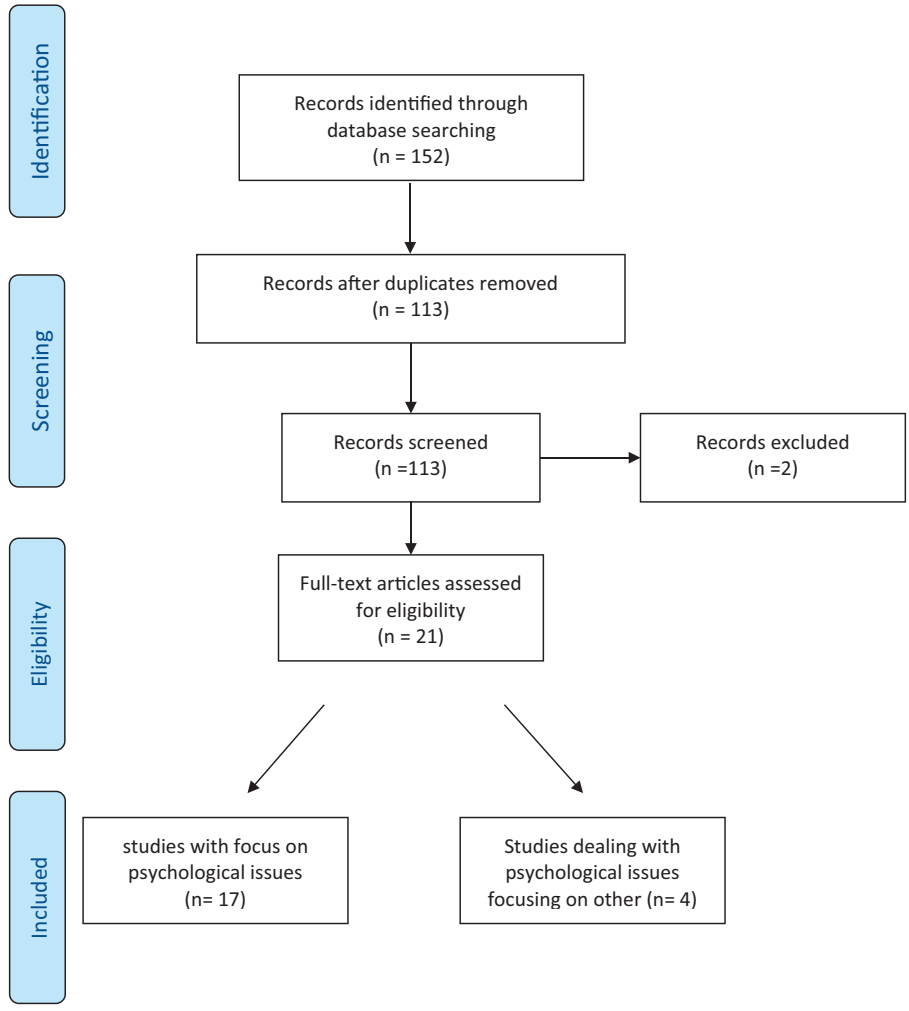

Figure 1. *Prisma flow diagram. Diagram of studies screened and included.*

Also, Supplemental Table 2 refers to indirect studies in which psychological aspects relevant for the SR were evaluated as additional variables related to other aspects of C1-INH–HAE, such as biologic and diagnostic workup and treatment strategies.

DISCUSSION

Psychological Aspects

In recent years, the scientific literature has shown a growing interest in studying psychological aspects associated with the illness experience of patients with C1-INH–HAE. In fact, the first studies on psychological aspects only began to emerge in 2010. In all of the studies examined, the majority of patients with C1-INH–HAE reported levels of psychological distress, identified by either high score values on rating scales or during conversations with the participants.

Anxiety and depression disorders were detected in the narratives[19,22] of patients and family caregivers as well as in *ad hoc* questionnaires administered to adult patients. These patients reported levels of anxiety and depression significantly higher than the normative sample.[22–24,26] Furthermore, these experiences are correlated negatively with patients' QoL, which is lower than average with regard to their mental health and social relationships,[22,27] and with respect to their work productivity.[1] A considerable percentage of individuals with C1-INH–HAE reported that living with the disease may affect their relationships and decisions, such as whether to have children[22,26,28] or whether to set out on a journey.[26] Patients also reported experiencing anxiety about having future attacks and the unpredictability with which they may occur. Anxiety also increased when the attack caused swelling of the glottis.[26,30]

Moreover, anxiety levels were found to be higher in child and adolescent patients (ages 6 to 18 years) for both episodic state anxiety and trait anxiety, which consist of a constant state of autonomic arousal.

Furthermore, the high levels of anxiety observed in these young patients were associated with a higher number of body areas affected by the attacks.[31] When concerning depression, the study carried out by Fouche *et al.*[24] found severe levels of depression among all 26 participants examined, whereas the study conducted by Bygum *et al.*[30] revealed symptoms of depression in 42% of the participants, which thus indicates that it is a common mental health problem that must be considered when treating patients with C1-INH–HAE. According to self-reported data gathered from patients, the main trigger of C1-INH–HAE attacks seems to be stress, followed by physical trauma.[7,20,32] When evaluated as a psychological variable that refers to the individual's perceived stress, 64% of the patients had stress scores higher than the standard population. Stress scores were also higher for individuals with C1-INH–HAE than for the control group subjects affected by other chronic diseases.[20,29]

Also, emotion regulation processes were evaluated within a group of pediatric subjects by exploring the levels of alexithymia and emotional awareness among children with C1-INH–HAE. Both alexithymia and emotional awareness are considered in the literature to be critical components of the emotion regulation process. The study conducted by Savarese *et al.*[21] revealed that alexithymia affects 84% of children with C1-INH–HAE and that this deficit correlates positively with the severity of the disease. Compared with control groups composed of children with other chronic pathologies, the deficit seems to be a common feature of all pediatric patients with a chronic disease. Finally, alexithymia correlated positively with the individual's perceived stress, which thus suggests that deficits in emotion regulation may translate into the perception of being less capable of coping with life events, which children with alexithymia perceive as being more stressful.[13]

The disease's psychological and social implications are also attributable to the difficulty of obtaining a correct diagnosis and complying with an effective therapeutic regimen due to treatment failure or the shortage or unavailability of medicines.[7,10,14] Although the correct diagnosis and effective medical treatment may significantly improve their QoL,[19,33] patients' predominant concern is the fear of transmitting C1-INH–HAE to their children, which thus indicates that, despite improvements in C1-INH–HAE treatments, it is widely perceived to be a disabling disease that not only decreases a patient's capacity to perform activities associated with daily living and negatively impacts his or her QoL.[33]

A qualitative study conducted by Freda *et al.*[19] on the narratives of parents of children with C1-INH–HAE shows that effective strategies for coping with their child's daily life problems were associated with how flexible they were in handling their triggers and attacks, and in implementing disease management strategies. This flexibility allows treatment to be adapted to the personal needs of patients without too many social and recreational limitations.[19] Patients who live with C1-INH–HAE may experience substantial psychosocial distress due to attack-related anxiety and the disappointment of being unable to participate in certain activities. The disease's long-term effects on the patient's lifestyle, emotional health, career, educational attainment, family life, and medical resource utilization have significant and lasting effects that may also have an impact on their caregivers' QoL.[7]

Diagnostic and Therapeutic Implications: The Need to Optimize Management of Patients with C1-INH–HAE

C1-INH–HAE is often a diagnostic challenge for physicians because its clinical heterogeneity may lead to a diagnostic delay (DD) and impair the therapeutic management. A retrospective analysis of Icatibant Outcome Survey (IOS) registry data for patients from the United Kingdom showed a median DD of 6.2 years,[33] whereas a study on a pediatric population with C1-INH–HAE found a median DD of 8 years.[28] DD and misdiagnosis may lead to unnecessary diagnostic and surgical procedures and may, in addition, interfere with the correct primary prevention of the attacks. Indeed, appropriate lifestyle modifications (such as avoiding mechanical trauma, specific exacerbating medications, and airway infections in children) may be useful in better managing the disease.[34,35] This is supported by the observation of Farkas,[35] that, in patients diagnosed before the onset of symptoms, initial manifestations occurred later, at the age of 6 years (rather than 4 years).

Moreover, because C1-INH–HAE is a potentially life-threatening disease, it is essential to instruct patients and their relatives about the first signs of laryngeal edema and the necessary procedures to treat it because the interval between the onset of symptoms and an acute risk of asphyxiation in adults, in particular, is usually long enough to allow for appropriate emergency interventions.[5] The mortality by asphyxiation rate is higher in patients with undiagnosed C1-INH–HAE,[6] which underscores the need to identify these patients and diagnose their condition as soon as possible.[36,37] However, the diagnostic phase could be slow and painful. The feelings of uncertainty combined with the attacks themselves and the dependence on medication, furthermore, could generate stress and add strain around family adaptation.[7] Indeed, according to Granero-Molina *et al.*,[10] C1-INH–HAE affects the QoL for both patients and families, and family caregivers may develop psychological problems as well.[10]

Several consensus documents for the management of C1-INH–HAE have been developed to reduce the physical severity and frequency of attacks.[38] There are two main treatment strategies: ODT and LTP.[39] In evaluating the need for introducing LTP as a treatment method, physicians should first consider factors such as attack frequency, availability of emergency therapy, timely access to medical care, number of emergency visits, and impact of the disease on patients' daily lives such as absenteeism from work or school.[40,41] LTP is used to prevent the onset of life-threatening attacks, which make it particularly warranted for patients with a history of upper airway edema.[40] In further support of this, it has been reported that reducing the frequency of C1-INH–HAE attacks also reduces the risk of upper airway edema.[40]

A recently published web-based survey by Banerji *et al.*[13] showed that a high frequency of attacks was generally associated with a greater disease burden, which included worse anxiety and depression (assessed by using the Hospital Anxiety and Depression Scale) as well as lower energy levels and greater difficulty in performing necessary daily activities (evaluated through the 12-Item Short Form Survey), which leads to increased work and activity impairment. They also reported a correlation between the attack site and the impact on work productivity and activity impairment by using the Hereditary Angioedema Quality of Life Questionnaire.[13] Specifically, attacks that exclusively affected the face were generally associated with higher absenteeism (26.5%), presenteeism (44.0%), and work productivity loss (48.2%) than attacks that affected other locations.[13] Activity impairment was highest among patients whose most recent attack affected the abdomen and throat (76.7%), and lowest in those whose attacks affected only the extremities (33.3%).[13] Also, mean Hereditary Angioedema Quality of Life Questionnaire total scores were generally lower among patients whose most recent attack involved the throat relative to attacks that involved only the extremities.[13]

In recent years, different drugs have been approved for LTP. Some of these agents are highly effective, whereas others have shown variable efficacy and are limited by potential adverse effects. For example, chronic use of androgen therapy for C1-INH–HAE prophylaxis was associated with significant adverse effects that further diminished HRQoL in study patients.[11,39] More than half of the patients who took androgens reported mood changes (59.7%), whereas nearly half reported agitation and sleeplessness or insomnia (45.6%).[11,39] Compared with patients who did not take androgens, patients with C1-INH–HAE and who received androgen scored significantly higher on the Hamilton Depression Inventory-Short Form (8.7 versus 7.4; $p < 0.001$).[25,42]

Furthermore, some ODT and LTP drugs require an intravenous infusion, which means that patients with C1-INH–HAE must go to emergency departments to receive medical treatment. Currently, the World Allergy Organization has agreed that self-administration for attacks and prophylaxis of C1-INH–HAE is the preferred method of treatment because of its proven effect in leading to a decrease in morbidity, absenteeism, cost, disease burden, and potential mortality. In addition, self-administration provides an increase in the patient's QoL.[43–45] Treatment options for self-administered therapy consist of plasma-derived C1-INH concentrate, icatibant, recombinant C1-INH, and lanadelumab.[39] Preventative treatment strategies have been shown to impact HRQoL in patients with C1-INH–HAE. Lumry *et al.*[47] evaluated the effect of LTP with intravenous injections of nanofiltered C1-INH concentrate on the HRQoL (as measured by the 36-Item Short Form Survey) of patients with C1-INH–HAE. The investigators reported an improvement in HRQoL in those who received preventive therapy compared with patients who received ODT only.[46,47]

The recent approval of subcutaneous C1-INH and lanadelumab has significantly broadened the armamentarium of physicians. A randomized, double-blind, dose-ranging, cross-over study by Weller *et al.*[48] observed HRQoL changes by using the Angioedema Quality of Life questionnaire in patients with C1-INH–HAE who received subcutaneous C1-INH with recombinant hyaluronidase for attack prophylaxis as well as improved Angioedema Quality of Life questionnaire scores after ~16 weeks of treatment. Lanadelumab, meanwhile, is a fully human monoclonal antibody, which is a highly specific inhibitor of plasma kallikrein, the enzyme involved in the formation of the bradykinin (the chief C1-INH–HAE pathogenetic mediator).[49] As a subcutaneous injection administered once every 2–4 weeks, lanadelumab may help address some of the limitations of existing prophylactic options (*i.e.*, tolerability issues, intravenous administration, and the need for frequent dosing schedules).[46] In a recent study by Banerji *et al.*,[50] a significant improvement in patient-reported HRQoL was demonstrated in patients treated with lanadelumab compared with a placebo.

Furthermore, this improvement exceeded that of the subcutaneous C1-INH with recombinant hyaluronidase for prophylaxis.[48] Christiansen *et al.*[51] conducted a survey that evaluated the burden of disease among 134 subjects with HAE (85 type I, 21 type II, and 28 with normal C1-INH) before and after the availability of newer, on-demand, and prophylactic treatments. Questions covered five domains: psychological and/or emotional status, ability to carry out daily activities, fear of suffocation, worry about their children inheriting HAE, and medication adverse effects.[51] The investigators found a substantial lessening of disease burden with the introduction of newer agents; they reported an overall improvement in all domains except worry about children inheriting the disease.[51]

CONCLUSION

Unrecognized or untreated C1-INH–HAE causes a significant burden of illness, which results in impaired QoL, increased health care costs, and decreased work productivity. These observations emphasize the importance of an early diagnosis of C1-INH–HAE and of prescribing an effective and tailored treatment regimen to prevent or reduce the frequency and severity of attacks.[27]

Limitations and Future Prospects

The analyzed studies highlight numerous psychological elements linked to emotional expression, anxiety, emotion regulation difficulties, and high stress levels in adult and pediatric patients affected by C1-INH–HAE. Despite this, there is no evidence of a causal relationship between intense emotions and C1-INH–HAE attacks. However, on the one hand, the literature confirms that stress may induce various physical diseases, on the other hand, it warns us against making simplistic statements about its incidence that do not take into account the complexity and multicausality of factors that contribute to C1-INH–HAE expression.

The implications of conveying to patients the belief that stress may induce the onset of a C1-INH–HAE attack can have controversial effects. Previous studies revealed how attempts at avoiding stress and other challenging emotions, which are unavoidable aspects of everyone's daily life, can have adverse effects on patients' ability to cope with the disease and on their QoL.[19,20] Therefore, reports on the patient's emotional state should be communicated between the physician and the patient, thus emphasizing the importance of increasing emotional awareness, expression, and regulation through targeted and personalized interventions.

REFERENCES

1. Bova M, De Feo G, Parente R, et al. Hereditary and acquired angioedema: heterogeneity of pathogenesis and clinical phenotypes. Int Arch Allergy Immunol. 2018; 175:126–135.
2. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. J Allergy Clin Immunol Pract. 2018; 6:1132–1141.
3. Bork K, Wulff K, Rossmann H, et al. Hereditary angioedema cosegregating with a novel kininogen 1 gene mutation changing the N-terminal cleavage site of bradykinin. Allergy. 2019; 74:2479–2481.
4. Farkas H, Zotter Z, Csuka D, et al. Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor – a long-term survey. Allergy. 2012; 67:1586–1593.
5. Bork K, Hardt J, Schicketanz KH, et al. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. Arch Intern Med. 2003; 163:1229–1235.
6. 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.
7. Bygum A, Aygören-Pürsün E, Beusterien K, et al. Burden of illness in hereditary angioedema: a conceptual model. Acta Derm Venereol. 2015; 95:706–710.
8. Huang SW. Results of an on-line survey of patients with hereditary angioedema. Allergy Asthma Proc. 2004; 25:127–131.
9. Cicardi M, Agostoni A. Hereditary angioedema. N Engl J Med. 1996; 334:1666–1667.
10. Granero-Molina J, Sánchez-Hernández F, Fernández-Sola C, et al. The diagnosis of hereditary angioedema: family caregivers' experiences. Clin Nurs Res. 2020; 29:117–126.
11. Banerji A. The burden of illness in patients with hereditary angioedema. Ann Allergy Asthma Immunol. 2013; 111:329–336.
12. Zotter Z, Csuka D, Szabó E, et al. The influence of trigger factors on hereditary angioedema due to C1- inhibitor deficiency. Orphanet J Rare Dis. 2014; 9:44.
13. Banerji A, Davis KH, Brown M, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. Ann Allergy Asthma Immunol. 2020; 124:600–607.
14. Longhurst H, Bygum A. The humanistic, societal, and pharmaco-economic burden of angioedema. Clin Rev Allergy Immunol. 2016; 51:230–239.
15. Germenis AE, Speletas M. The genetics of hereditary angioedema: the iceberg slowly emerges. J Angioedema. 2016; 2:8–17.
16. Kaplan AP, Maas C. The search for biomarkers in hereditary angioedema. Front Med. 2017; 4:206.
17. Moher D, Shamsee L, Clarke M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015; 4:1.
18. Aabom A, Andersen KE, Perez-Fernández E, et al. Health-related quality of life in Danish patients with hereditary angioedema. Acta Dermato-Venereol. 2015; 95:225–226.
19. Freda MF, Savarese L, Dolce P, et al. Caregivers' sensemaking of children's hereditary angioedema: a semiotic narrative analysis of the sense of grip on the disease. Front Psych. 2019; 10:2609.
20. Freda MF, Savarese L, Bova M, et al. Stress and psychological factors in the variable clinical phenotype of hereditary angioedema in children: a pilot study. Pediatr Allergy Immunol. 2016; 29:6–12.
21. Savarese L, Bova M, De Falco R, et al. Emotional processes and stress in children affected by hereditary angioedema with C1-inhibitor deficiency: a multicenter, prospective study. Orphanet J Rare Dis. 2018; 13:115.
22. Kuman Tunçel Ö, Gökmen N, Demir E, et al. The impact of hereditary angioedema on quality of life and family planning decisions. Int J Psychiatry Med. 2019; 54:377–394.
23. Liu S, Wang X, Xu Y, et al. Risk factors for diagnostic delay in Chinese patients with hereditary angioedema. Allergy Asthma Proc. 2019; 40:343–349.
24. Fouche AS, Saunders E, Craig T. Depression and anxiety in patients with hereditary angioedema. Ann Allergy Asthma Immunol. 2014; 112:371–375.
25. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc. 2010; 31:407–414.
26. Caballero T, Sala-Cunill A, Cancian M, et al. Current status of implementation of self-administration training in various regions of Europe, Canada and the USA in the management of hereditary angioedema. Int Arch Allergy Immunol. 2013; 161 (suppl):10–16.
27. Bernstein JA. HAE update: epidemiology and burden of disease. Allergy Asthma Proc. 2013; 34:3–6.
28. Christiansen SC, Davis DK, Castaldo AJ, et al. Pediatric hereditary angioedema: onset, diagnostic delay, and disease severity. Clin Pediatr (Phila). 2016; 55:935–942.

29. Toscani M, Riedl M. Meeting the challenges and burdens associated with hereditary angioedema. Manag Care. 2011; 20:44–51.
30. Bygum A, Aygören-Pürsün E, Caballero T, et al. The hereditary angioedema burden of illness study in Europe (HAE-BOIS-Europe): background and methodology. BMC Dermatol. 2012; 12:4.
31. Kessel A, Farkas H, Kivity S, et al. The relationship between anxiety and quality of life in children with hereditary angioedema. Pediatr Allergy Immunol. 2017; 28:692–698.
32. Nygren A, Nordenfelt P, Lindfors A, et al. Swedish children with hereditary angioedema report good overall health and quality of life despite symptoms. Acta Paediatr. 2016; 105:529–534.
33. Longhurst HJ, Dempster J, Lorenzo L, et al. Real-world outcomes in hereditary angioedema: first experience from the Icatibant Outcome Survey in the United Kingdom. Allergy Asthma Clin Immunol. 2018; 14:28.
34. FüSt G, Széplaki G, Csuka D, et al. Increase in the yearly attack frequency in HAE patient treated with danazol for 6 years. 6th C1-inhibitor Deficiency Workshop. Budapest, Hungary 2009.
35. Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. Allergy Asthma Clin Immunol. 2010; 6:18.
36. Landerman NS. Hereditary angioneurotic edema. I. Case reports and review of the literature. J Allergy. 1962; 33:316–329.
37. Cicardi M, Bergamaschini L, Marasini B, et al. Hereditary angioedema: an appraisal of 104 cases. Am J Med Sci. 1982; 284:2–9.
38. Craig T, Aygören-Pürsün E, Bork K, et al. WAO guideline for the management of hereditary angioedema. World Allergy Organ J. 2012; 5:182–199.
39. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. J Allergy Clin Immunol Pract. 2013; 1:458-467.
40. Farkas H, Management of upper airway edema caused by hereditary angioedema. Allergy Asthma Clin Immunol. 2010; 6:19.
41. Zuraw BL. Hereditary angiodema: a current state-of-the-art review, IV: short-and long-term treatment of hereditary angioedema: out with the old and in with the new? Ann Allergy Asthma Immunol. 2008; 100(suppl 2):S13–S18.
42. Cardarelli W. Managed care implications of hereditary angioedema. Am J Manag Care. 2013; 19(suppl):s119–s124.
43. Hemperly SE, Agarwal NS, Xu YY, et al. Recent advances in the management of hereditary angioedema. J Am Osteopath Assoc. 2013; 113:546–555.
44. Cicardi M, Craig TJ, Martinez-Saguer I, et al. Review of recent guidelines and consensus statements on hereditary angioedema therapy with focus on self-administration. Int Arch Allergy Immunol. 2013; 161(suppl 1):3-9.
45. Wang A, Fouche A, Craig TJ. Patients perception of self-administrated medication in the treatment of hereditary angioedema. Ann Allergy Asthma Immunol. 2015; 115:120–125.
46. Busse PJ, Farkas H, Banerji A, et al. Lanadelumab for the prophylactic treatment of hereditary angioedema with C1 inhibitor deficiency: a review of preclinical and phase I studies. BioDrugs. 2019; 33:33–43.
47. Lumry WR, Miller DP, Newcomer S, et al. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy Asthma Proc. 2014; 35:371–376.
48. Weller K, Maurer M, Fridman M, et al. Health-related quality of life with hereditary angioedema following prophylaxis with subcutaneous C1-inhibitor with recombinant hyaluronidase. Allergy Asthma Proc. 2017; 38:143–151.
49. Kenniston JA, Faucette RR, Martik D, et al. Inhibition of plasma kallikrein by a highly specific active site blocking antibody. J Biol Chem. 2014; 289:23596–23608.
50. Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. JAMA. 2018; 320:2108–2121.
51. Christiansen SC, Bygum A, Banerji A, et al. Before and after, the impact of available on-demand treatment for HAE. Allergy Asthma Proc. 2015; 36:145–150. doi:10.2500/aap.2015.36.3831 □