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Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients

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ABSTRACT

Background: Hereditary angioedema (HAE) is a rare and potentially life-threatening disease. New specific treatments are available.

Objective: To identify patients' features and patients' best therapeutic option.

Methods: A 1-year, multicenter, retrospective study was performed. The primary objective was to examine the clinical presentation of HAE. Secondary objectives included patient characteristics, management of HAE over 12 months, and health-related quality of life using the SF-36v2 questionnaire.

Results: One hundred ninety-three patients were included, and 69.4% were women. In the 12-month period, the mean number of HAE attacks was 7.6. Among the 568 reported attacks, localizations were the abdomen (57.1%), peripheral limbs (42.5%), upper airway (7.9%), and face (6.9%); 31.6% of attacks were severe and occurred statistically more often in women ($P < .02$). Compared with a population of allergic patients, all age- and sex-adjusted scores were significantly lower in patients with HAE ($P < .05$) except for the physical component summary. Health-related quality of life negatively correlated with the annual number of attacks and was markedly altered for patients having more than 5 attacks per year ($P < .05$ for all dimensions).

Conclusion: HAE is a severe disease that places a heavy burden on quality of life.

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Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disease with an estimated prevalence of 1 per 50 to 100,000 inhabitants in Europe.^{1,2} It was first reported in 1882 by Quincke³ who described a clinical presentation of peripheral edema and abdominal pain. HAE types I and II are associated with mutations

located on the *SERPINE1* gene coding for C1 inhibitor (C1-INH).⁴ Type I is characterized by decreased synthesis of functionally intact C1-INH, resulting in lower C1-INH concentrations. Patients with type II exhibit normal or even elevated concentrations of C1-INH, but the protein is functionally defective. Patients with HAE have recurrent episodes of edema that commonly occur in the skin,

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abdomen, and larynx. Upper airway or laryngeal attacks are potentially life-threatening. HAE type I and II attacks are a result of decreased levels, or function, of C1-INH, leading to elevated bradykinin levels that trigger increased vascular permeability and edema.^{5–7} The epidemiologic data on this disease are sparse. The first French case of HAE with a demonstrated C1-INH deficiency was published in 1970.⁸ In 1995, the characteristics of 33 French patients with HAE were reported.⁹ In 1991, the creation of a French national registry was advocated to identify the morbidity and mortality associated with the disease and to better treat patients.¹⁰ Thus, this national study was performed to identify, characterize, and provide epidemiologic data (eg, clinical presentation, management of HAE, and health-related quality of life [HRQoL]) in French patients affected by HAE.

Methods

Design Overview

For this 1-year, observational, multicenter, retrospective study, patients were recruited by 19 medical centers treating patients with HAE and belonging to the French National Reference Center for HAE (CREAK) in France from January through December 2010. Patients included in the study were those diagnosed with any form of HAE. Informed oral consent was required from all patients; for patients younger than 18 years, written consent from a parent or guardian was required. The study was approved by the Advisory Committee on Information Processing in Material Research in the Field of Health and by the National Commission for Computing and Liberties.

Study Objectives

The primary objective was to examine the clinical presentation of HAE. Secondary objectives included patient characteristics, management of HAE over 12 months (acute and prophylactic treatments), and HRQoL.

Outcome Measurements

During a routine visit, after oral consent, information was collected from diaries the patients kept or from memory. For each included patient, the investigator had to complete a medical questionnaire and give the patient a self-assessment questionnaire. The investigator collected sociodemographic data, baseline characteristics (age at first attack and at diagnosis), HAE, occurrence of severe events during the patient's life in relation to HAE attacks, the number of attacks during the past year, and the prophylactic treatment of the patient. Patients were asked to complete the following information in the self-assessment questionnaire: history and description of attacks over a 1-year period, medical treatment of the attack and, if left untreated, the reasons not to treat the attacks, hospitalizations, and sick leave. Severity of attacks was related to a patient's disability. HRQoL was assessed with the SF-36 v2 questionnaire and results in the HAE population were compared with those of an allergic population^{11,12} after adjustment for age and sex.

Statistical Analysis

The significance level was 5% in 2-sided tests for comparisons between groups. For comparative analysis, the Pearson χ^2 test was used for qualitative variables unless the theoretical (estimated) sample size in any cell was less than 5, in which case the Yates continuity correction was applied or the Fisher exact test was used. For quantitative variables, the Student *t* test or analysis of variance was performed. Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, North Carolina).

Results

Patient Characteristics and Clinical History

One hundred ninety-three patients HAE were included (Table 1), and 13 had HAE type II. Most patients were women (69.4%). The mean age of patients at inclusion was 39 ± 17 years. Few patients (4.6%) were 16 years or younger. The mean age at the time of the first symptoms was 14 years. When diagnosis was made after the initial symptoms, the mean time from onset of initial symptoms to diagnosis was 12 years. Some patients (14.9%) had no familial history of HAE.

Nearly 85% of patients had experienced at least 1 severe event from an HAE attack. In particular, 111 (56.6%) reported at least 1 episode of laryngeal edema during the course of the disease. Severe HAE attacks resulted in 48 patients (24.5%) undergoing at least 1 abdominal surgical intervention, 17 (9%) were hospitalized at least once in the intensive care unit, and 7 (3.6%) had undergone tracheotomy (or intubation) at least once.

More than half (62.8%) of the study patients ($n = 123$) were receiving long-term prophylactic treatment. Patients were treated with danazol (59.3%), tranexamic acid (29.3%), or a combination of these drugs (11.4%).

One-Year Retrospective Data

The mean annual number of HAE attacks was 7.6 (median 5; Table 2). Among the 564 attacks reported by the patients, 31.6% were severe. The mean annual number of severe attacks was 2.4 (calculated as 45.9% of the mean annual number of attacks).

In addition, during the year, 34.4% of women had had at least 1 severe attack vs 23.6% of men ($P < .02$).

The 193 patients who completed a self-assessment questionnaire reported 564 HAE attacks during the 12-month study period (Table 2). Of the 564 attacks, 57.1% were abdominal, 42.5% were peripheral, 7.9% involved the mouth, throat, or airways, and 6.9% involved the face (total exceeds 100% because an attack may involve different locations).

A triggering factor was reported for 76.6% of patients, with emotional stress being the most frequent. The existence of a prodrome was reported by 40.3% of patients, mainly fatigue (51.3%).

On-demand medical treatment was required for 421 of 553 attacks (76.8%) for which this information was reported. Treatments were tranexamic acid for 57.1% of attacks, icatibant for 12.7%, and C1-INH concentrate for 13.7% of patients. Self-administration (by the patient or a family member) was performed in 63% of cases using icatibant and in 16.4% using C1-INH concentrate. The median period from attack onset to administration of treatment was 1 hour for tranexamic acid and 4 hours for icatibant (Shire Human Genetic Therapies, Boulogne-Billancourt, France) and C1-INH concentrate.

Hospitalization was required for 63 of 558 (11.3%) for whom this information was reported. Of those patients who were hospitalized, 9 of 59 (15.3%) for whom this information was reported were admitted to the intensive care unit. None of them required intubation.

Table 1

Characteristics of patients with hereditary angioedema ($n = 193$)

Women, n (%)	134 (69.4)
Age at inclusion (y), mean $\pm$ SD	39 ± 17
Age at time of first symptom (y), mean $\pm$ SD	14 ± 10
≥ 1 laryngeal edema, n (%)	111 (56.6)
≥ 1 abdominal surgery, n (%) ^a	48 (24.5)
≥ 1 intubation or tracheotomy, n (%) ^a	7 (3.6)
≥ 1 hospitalization, n (%) ^a	112 (57)

Abbreviation: SD, standard deviation.

^aFor an angioedema attack.

Table 2

Characteristics of hereditary angioedema attacks that occurred during the past 12 months (n = 568)

Attacks per year, mean $\pm$ SD	7.6 $\pm$ 11
Attacks per year, median (range)	5 (0–60)
Abdomen, n (%)	324 (57.1)
Peripheral limbs, n (%)	241 (42.5)
Upper airways, n (%)	45 (7.9)
Face, n (%)	39 (6.9)
Severe attacks according to patient, n (%)	182 (31.6)
Attacks treated with specific drug, n (%) ^a	424 (76.7)
Hospitalizations, n (%)	63 (11.3)

Abbreviation: SD, standard deviation.

^aTranexamic acid, icatibant, or C1 inhibitor concentrate.

Sick leave from work (mean period 5 days) was certified for 73 of 524 attacks (13.9%) for which this information was reported.

Quality of Life

Compared with French population norms,¹² scores were significantly lower for patients with HAE ($P < .0001$; Fig 1). Compared with a population of patients with allergies,¹³ all age- and sex-adjusted scores were significantly lower for patients with HAE ($P < .05$). HRQoL was markedly altered for patients having more than 5 attacks per year compared with asymptomatic patients ($P < .05$; Fig 2). Patients having more than 12 attacks also had an altered HRQoL, but scores were not significantly lower than in patients having more than 5 attacks.

Discussion

This is the first time that a so large study has been performed in France. Important information was obtained about French patients. In France, there are nearly 650 to 1,300 patients with HAE based on a disease prevalence of 1 in 50 to 100,000 inhabitants.^{1,2} This cohort presents similar characteristics as those in other countries and some differences. Thus, the mean delay from the first symptom to the diagnosis of HAE was 12 years in this study. This is similar to the 13.1 years observed in Spain in 2005¹ and shorter than the 16.3 years in a Danish study.¹⁴ HAE is an autosomal dominant disease, which would imply that men and women are equally affected. However, the present study found a predominance of female patients, which has been reported in other studies.^{14–16} One explanation for this could be that women have more attacks than men, as reported in some studies¹⁵ and the present study. Indeed, 34.4% and 23.6% of the attacks reported by women and men, respectively, were severe ($P < .02$). This may be related to the fact that some female patients with HAE respond to physiologically and/or pharmacologically increased serum estrogen with an increased frequency of attacks.¹⁷ Moreover, Visy et al¹⁸ found a significant

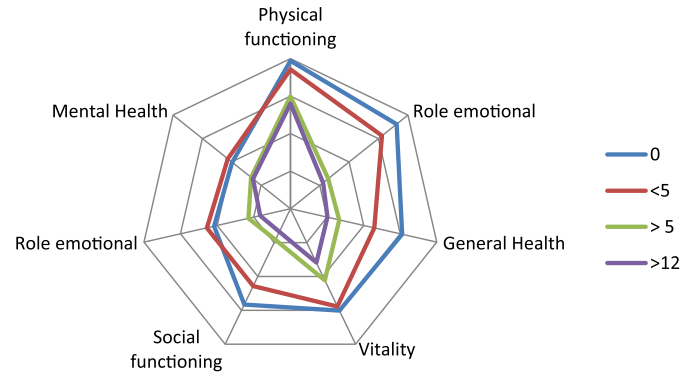


Figure 2. Mean (standard deviation) health-related quality-of-life scores of patients with hereditary angioedema according to the number of attacks in the previous year.

correlation between attack frequency and serum progesterone levels in female patients with HAE, but not in male patients.

First symptoms occurred at the time of puberty (14 years). This has been observed in other cohorts.^{14,15,19} In contrast to Bork et al¹⁵ who reported that early onset is associated with a more severe form of the disease, the authors found no difference in the severity of attacks according to the age at first symptoms.

The annual number of attacks in the present population was smaller than those reported in other countries. The mean was 7.6 (11) and the median was 5 (0–60) vs medians of 10.7 (0–72) in Denmark¹⁴ and 12 (0–350) in the United States.¹⁶ This may be explained in part by the fact that more French patients use prophylactic treatment: 62.8% vs 30% in Denmark¹⁴ and 49.5% in the United States.¹⁶ Of the 568 attacks analyzed, 42.5% were peripheral, 57.1% were abdominal, 6.9% involved the face, and 7.9% involved the mouth, throat, or airways. German and Italian studies have noted a slightly different distribution with fewer abdominal attacks. In Germany, of 131,110 attacks, 45% were peripheral, 48% were abdominal, 1.6% involved the face, and 0.9% were laryngeal.¹⁵ In Italy, of 1,532 attacks, 45.5% were peripheral, 33% were abdominal, and 6% were laryngeal.²⁰ Laryngeal edema is a life-threatening manifestation of HAE, with an estimated mortality of 25% in the absence of any specific treatment.^{1,2} Historically, one third of patients died before the fifth decade of life from asphyxia caused by laryngeal edema.²¹ In the present study, 56.6% of patients reported at least 1 laryngeal edema during their lifetime. The frequency has been evaluated at 1 per 125 attacks in a retrospective study.²²

Thirty-two percent of attacks were considered severe by the patients. Severe attacks had to be treated with specific drugs according to different consensus and guidelines. At the time of this survey, icatibant and C1-INH (Berinert, King of Prussia, PA) were available in France, and 26.4% of the total attacks were treated with these 2 specific drugs. Only a few severe attacks were not treated properly (17% of severe attacks). The CREAK network is ensuring that each patient with HAE can have a specific treatment available at home (icatibant or a C1-INH concentrate [Berinert; CSL Behring, King of Prussia, Pennsylvania] for rapid administration (even self-administration) in the case of a severe attack. Thus, only 11.3% of attacks required hospitalization. Icatibant was self-administered by 63% of patients who used it, with a median delay of 4 hours after the start of the attack.

A triggering factor, mainly stress, for the attacks was found in 71.5% of patients and prodromes in 41.2%, mainly fatigue. A previous study (46 patients) also reported that fatigue was often reported as a prodrome, as were a reticular rash and muscle pain.²³ Others have reported a relation between stress and the occurrences of attacks.²⁴

Prophylactic treatment concerned 62.82% of the present patients. The usual indications for long-term prophylaxis are the appearance of more than 1 attack per month or being indisposed

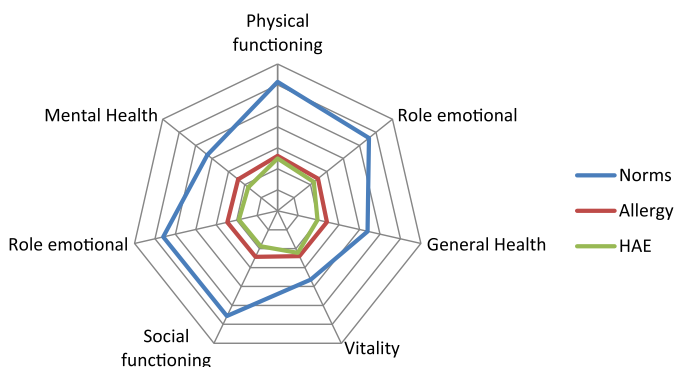


Figure 1. Mean health-related quality-of-life scores of patients with hereditary angioedema (HAE) compared with an age- and sex-adjusted group of control patients³⁰ and those with allergies (SF36-v2).

more than 5 days per month, a history of laryngeal edema, or inaccessibility of treatment for acute attacks.^{25,26} Danazol was prescribed to 59.3% of patients and tranexamic acid to 29.3%. Danazol is well known for having numerous metabolic, hormonal, and clinical side effects, especially in women, including weight gain, virilization, hirsutism, hoarse voice, irregularity of menstrual cycles, etc,²⁷ and thus was more frequently prescribed to male than to female patients. In France, within the CREAK network, physicians prescribe tranexamic acid as first-line prophylactic treatment owing to its good tolerance.²⁸ In Italy, only 13.8% of patients receive tranexamic acid.²⁰ Tranexamic acid is less efficient than danazol but its good tolerance is interesting, especially in women. Only 1 patient was receiving long-term prophylaxis with C1-INH concentrate. This practice has been reported by several European investigators and a C1-INH concentrate (Cinryze, ViroPharma Inc, Exton, Pennsylvania) has been approved in the European Union and the United States for use as long-term treatment.²⁹

The burden of HAE attacks is substantial. It is known that patients with HAE have a decreased HRQoL. In the United States, Lumry et al¹⁶ used an SF-12 questionnaire and reported decreased physical and mental component summaries (43.7 and 42.6, respectively) compared with a normal population ($P < .001$). In Brazil, Gomide et al³⁰ tested 35 patients with an SF-36 questionnaire; they reported that 90.4% of patients had a score below 70. The present study shows that HAE dramatically affects HRQoL compared with French population norms.¹² Patients with HAE also are more affected than patients with chronic allergy. Patients' HRQoL is inversely correlated to the number of annual attacks, with HRQoL clearly altered for patients with 5 or more attacks per year. This fact raises the question of the indication of long-term prophylaxis and suggests that a frequency of 5 or more attacks per year (and not the usual 12 per year) could be a good cutoff to discuss starting long-term prophylaxis. The unequivocal alteration of HRQoL supports that all attacks, no matter the location, are eligible for treatment.³¹ Two studies have reported that the use of C1-INH concentrate in case of attack is associated with an improvement of HRQoL.^{32,33}

The present study has some limitations, such as its retrospective nature and the potential biases associated with this kind of study. The objectives were to provide epidemiologic data on HAE, but the included population may not be a representative sample of all French patients with HAE. Some patients could be underdiagnosed because the attacks are mild and thus not reported, and/or the physicians may not be aware of the disease because of its rarity, leading to misdiagnosis. The present sample may be biased because the patients who are not managed in the reference centers are undertreated and may have a worse HRQoL. Conversely, underdiagnosed patients may have a milder form of the disease (and not be managed by the reference centers) and a better HRQoL.

These 2 mechanisms could cancel each other out. Moreover, this study was conducted among hospital expert centers. However, these centers are the French reference centers for the management of this disease and most diagnosed patients in France consult at least once a year in these centers. The patients were supposed to report all the attacks they had in a 1-year period. This may be biased because patients may not have remembered all the attacks they had; they may have reported only the most severe ones. However, the results are not very different from those of other studies.^{14–16,20}

In conclusion, this study shows that patients with HAE have a large number of attacks per year, some of them severe and life-threatening. The burden of the disease is substantial, with a decreased HRQoL, especially in patients with more than 5 attacks per year. Based on this study, the authors provide some recommendations for treating this population.

- Physicians need to be educated in the availability of self-administered treatment options (icatibant and C1-INH concentrate).

- Physicians need to be made more aware of HAE to avoid misdiagnosis, possibly leading to unnecessary treatments such as surgical procedures.
- Patients with suspected HAE attacks should be referred to specialist centers to be diagnosed and receive optimal treatment.
- Physicians need to recognize that HRQoL is decreased in patients with more than 5 HAE attacks per year.

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