

CLINICAL REPORT

Burden of Illness in Hereditary Angioedema: A Conceptual Model

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The objective of the Hereditary Angioedema Burden of Illness Study in Europe was to assess the real-world experience of hereditary angioedema (HAE) from the patient perspective. Based on open-ended qualitative interviews with 30 patients from Spain, Germany and Denmark, 5 key themes emerged characterizing the impact of HAE on health-related quality of life (HRQoL): (i) unnecessary treatments and procedures, (ii) symptom triggers, (iii) attack impacts, (iv) caregiver impacts, and (v) long-term impacts. Patients for example experience unnecessary medical procedures due to diagnostic delays; anxiety and fear about attacks, and passing HAE to children; reduced work/school productivity; and limited career/educational achievement. Patient caregivers also experience worry and work/activity interruption during the attacks. In conclusion, a conceptual model was developed illustrating the hypothesized relationships among the wide-ranging short- and long-term HRQoL impacts of HAE. These findings can be used to highlight important issues in clinical management, raise awareness of the patients' experience among policymakers and help guide measurement of HRQoL outcomes in future studies in HAE. Key words: burden of illness; conceptual model; health-related quality of life; hereditary angioedema; HAE; C1-inhibitor deficiency.

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Hereditary angioedema (HAE), a rare and potentially life-threatening disorder caused by C1-inhibitor deficiency, is characterized by spontaneous, recurrent attacks of swelling in various regions of the body (1, 2). During an HAE attack, patients may experience disfigurement, severe pain and inability to perform daily activities. Symptoms typically last for 1–4 days and frequency may range from almost none to 1 every 3 days (3, 4). Many patients have ancestors who died of asphyxiation due to laryngeal swelling, causing the patients to live in constant fear (3–6).

HAE treatment aims to reduce the physical severity and frequency of attacks, and several consensus documents for the management of HAE have been developed (7–11). However, little qualitative research has been conducted focusing on health outcomes from the patient's perspective, especially among adolescents and young adults. Conceptual models can be a useful way to illustrate the full range of ways in which a particular disease affects health-related quality of life (HRQoL) (12). Conceptual models developed in the patient-reported outcomes (PRO) field are detailed models that can be used to identify important concepts that could be measured as end-points in a clinical study and generally include the domains of physical, social and psychological functioning (13).

The Hereditary Angioedema Burden of Illness Study in Europe (HAE-BOIS-Europe) was a cross-sectional study undertaken to capture the HRQoL and economic burden of HAE comprehensively from the patient perspective. The study contained both quantitative and qualitative methodologies (14). This article focuses on the findings from the qualitative component, which involved one-on-one, open-ended interviews with HAE patients. The data from these interviews were used to guide the development of a conceptual model illustrating the impact of HAE from the patient perspective.

MATERIALS AND METHODS

The HAE-BOIS-Europe was conducted in Spain, Germany and Denmark, between May and December 2011. The 2 study components were: (i) a one-time web- or paper-based survey on the humanistic and economic burden of HAE (14–16); and (ii) open-ended patient interviews. Interviews were conducted with 10 participants with HAE per country. A sample of 30 participants was selected based on an industry task force report generally recommending a sample size of 20–30 participants for qualitative research (17). Interview participants were selected from clinical practice centres of excellence, taking a purposive sampling approach with an aim to recruit a mix of participants based on gender, age, disease severity, attack frequency, location of swelling and treatment type. To be eligible, participants had to be at least 12 years of age, with HAE Type 1 or 2. The full methodology is described in Bygum et al. in 2012 (14).

The interviews were conducted over the telephone in the local language by an interviewer trained in qualitative research (by the research group Oxford Outcomes). Interviewers followed

a semi-structured interview guide consisting of open-ended questions with additional probing questions as needed for further clarification of responses. The interview guide had 4 parts, with questions on demographics, clinical characteristics, the impact of HAE on daily life during attacks and in between attacks, and treatment history. On average, the interviews lasted approximately 30 min. Interviews were audio-recorded, transcribed verbatim, and translated into English.

Analysis involved a repeated review of the transcripts and was modelled after the framework approach, an applied qualitative analysis methodology, in which coded text, where the text is labelled into categories, is organized in a table by each individual respondent so that the context of the individual's views is not lost (18, 19). Analysis involved deduction to answer the *a priori* research questions; specifically, what is the impact of attacks on daily activities, and what is the impact of HAE when not having an acute attack. An inductive approach, in which categories or themes are identified based on the data and used to build theory, was used to identify all additional key themes. A conceptual model was developed, summarizing the themes identified and the hypothesized relationships among them. The conceptual model was reviewed and further refined and finalized by all of the authors in a consensus meeting.

RESULTS

Demographic and clinical characteristics.

Among the 30 participants, 18 (60%) were females, the mean age was 41 years (range 15–71 years; 5 (17%) aged 25 years or younger) and 20 (67%) were employed full- or part-time or were in education. These results were similar to those obtained in the quantitative study, with 60% of patients being female, a mean age of 43 years and 73% employed full- or part-time or studying (15, 16). Participants first experienced HAE symptoms at a mean \pm SD of 31.1 ± 16.0 years ago and received their HAE diagnosis 14.9 ± 9.4 years ago. Twenty participants (71%) had had an HAE attack within the past 30 days. The most common body parts affected by the last attack were the abdomen and extremities, each reported by 12 people (41%). Twelve participants (41%) reported that their attack lasted 1–2 days and 8 (28%) reported that it lasted less than 12 h, also comparable to the quantitative study (15). Six (20%) reported their overall health as “fair” as opposed to “good” or “better” (Table I).

Burden of illness

Fig. 1 shows the key themes that were identified, which were consistent across the 3 countries, and the hypothesized relationships among them. The qualitative analysis of the

data yielded 5 main areas, which characterize the burden of HAE: unnecessary treatments and procedures, symptom triggers, attack impacts, caregiver impacts and long-term impacts.

Unnecessary treatments and procedures. Many participants underwent unnecessary treatments and procedures while awaiting an accurate diagnosis. This included treatment for arthritis, appendicitis, food allergies and stomach ulcers. Several participants had unnecessary surgeries for these conditions, and now

Table I. Demographic and clinical characteristics

	Overall (n=30)	Spain (n=10)	Germany (n=10)	Denmark (n=10)
Female, n (%)	18 (60)	6 (60)	6 (60)	6 (60)
Age, years, mean \pm SD	41.0 \pm 15.4	42.0 \pm 14.6	35.0 \pm 12.3	47.0 \pm 18.0
Age range, n (%)				
15–25 years	5 (17)	1 (10)	2 (20)	2 (20)
26–45 years	13 (43)	5 (50)	7 (70)	1 (10)
46–65 years	9 (30)	3 (30)	1 (10)	5 (50)
66–71 years	3 (10)	1 (10)	0 (0)	2 (20)
Highest education achieved, n (%)				
Less than high-school	3 (10)	1 (10)	1 (10)	1 (10)
High-school diploma	8 (27)	3 (30)	4 (40)	1 (10)
Technical/vocational	8 (27)	1 (10)	3 (30)	4 (40)
University coursework/degree	9 (30)	4 (40)	2 (20)	3 (30)
Advanced degree	2 (7)	1 (10)	0 (0)	1 (10)
Employment status, n (%)				
Employed full-time	15 (50)	4 (40)	6 (60)	5 (50)
Employed part-time	3 (10)	1 (10)	0 (0)	2 (20)
Student	2 (7)	1 (10)	0 (0)	1 (10)
Unemployed	3 (10)	2 (20)	1 (10)	0 (0)
Retired	4 (13)	1 (10)	1 (10)	2 (20)
Other ^a	3 (10)	1 (10)	2 (20)	0 (0)
Years since first experiencing HAE symptoms, mean \pm SD	31.1 \pm 16.0	28.0 \pm 14.3 ^b	26.3 \pm 14.8	38.7 \pm 17.2
Years since receiving HAE diagnosis, mean \pm SD	14.9 \pm 9.4	16.5 \pm 14.3	17.4 \pm 9.7	13.8 \pm 11.5
Time since last attack, n (%)				
0–30 days	20 (71)	5 (56)	9 (90)	6 (67)
1–3 months	2 (7)	1 (11)	0 (0)	1 (11)
3–6 months	5 (18)	3 (33)	1 (10)	1 (11)
>6 months ago	1 (4)	0 (0)	0 (0)	1 (11)
Missing	2	1	0	1
Site of last attack, n (%)				
Abdomen	12 (41)	1 (11)	5 (50)	6 (60)
Extremity	12 (41)	4 (44)	5 (50)	3 (30)
Genitals	1 (3)	1 (11)	0	0 (0)
More than one site	4 (14)	3 (33)	0	1 (10)
Missing	1	1	0	0
Duration of attack, n (%)				
<12 h	8 (28)	2 (20)	3 (33)	2 (20)
12–24 h	5 (17)	2 (20)	1 (11)	3 (50)
1–2 days	12 (41)	4 (40)	5 (56)	3 (30)
>2–3 days	4 (14)	2 (20)	0 (0)	0 (0)
>3 days	2 (7)	0 (0)	0 (0)	2 (20)
Missing	1	0	1	0
Overall health, n (%)				
Excellent	5 (17)	1 (10)	2 (20)	2 (20)
Very good	5 (17)	1 (10)	1 (10)	3 (30)
Good	14 (47)	7 (70)	5 (50)	2 (20)
Fair	6 (20)	1 (10)	2 (20)	3 (30)
Poor	0 (0)	0 (0)	0 (0)	0 (0)

^aMaternity leave, disability, and self-employed (full-time/part-time unspecified). ^bResponse missing from one participant. SD: standard deviation; HAE: hereditary angioedema.

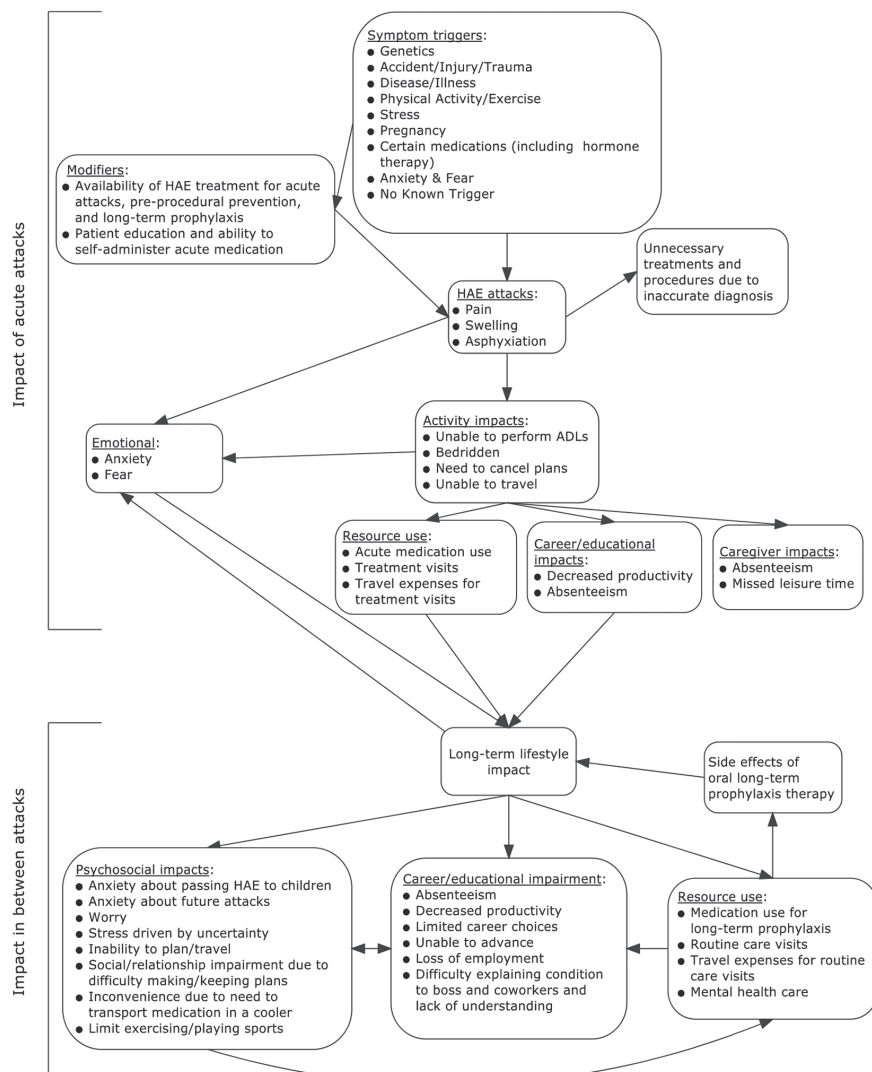


Fig. 1. Conceptual model. ADL: activities of daily living; HAE: hereditary angioedema.

have permanent scars. Participants stressed a need for greater awareness of HAE among clinicians and the general public. Table S1¹ presents selected quotes referring to unnecessary testing and treatments.

Symptom triggers. During acute attacks, participants experienced pain and swelling, which may have developed spontaneously, but was often preceded by accidents, illness, exercise, stress, or hormone changes. Triggers included knitting, gardening, falling while skiing, wearing high heels, catching a cold, hormone changes and stressful days or phases of life. Table S1¹ presents selected quotes referring to symptom triggers.

Attack impacts. Table S11¹ presents selected quotes referring to attack impacts. Attack symptoms included pain, swelling, and asphyxiation. Attacks have a substantial impact on daily activities, including the ability to perform household tasks, drive, participate in family activities, travel, or follow through on plans; some participants had been bedridden during attacks. The duration of activity disruption varied, but in many cases lasted 1–2 days. Participants largely considered abdominal attacks to involve the most severe pain. They could last for several days,

and be accompanied by vomiting, and may have forced the participant to be confined to bed. Swollen feet may also prevent the participant from being able to get out of bed, but participants generally considered extremity attacks to be less painful, though not necessarily less severe. Extremity attacks prevented participants from being able to do daily tasks involving the hands and feet, such as using a computer or driving.

The inability to perform normal activities during attacks caused interruption to participants' work or schooling, including absenteeism and decreased productivity. Participants mentioned that there are job tasks that they are unable to perform when they are having an attack, and attacks often required participants to take time off from their job. One participant mentioned that he had to be prepared to work from home or the hospital at any time because there were times when he could not be absent from his work for any reason.

Participants felt a great deal of emotional distress during attacks. Participants were anxious and fearful of the attack getting worse or potentially not being able to breathe. They feared that they would not be able to get to the hospital in time in the event of a laryngeal attack. Patients also experienced anxiety due to activity limitations during attacks, such as not being able to participate in family activities.

Attack modifiers. Symptom modifiers included the availability of treatment for acute attacks, pre-procedural prophylaxis, and long-term prophylaxis, and patient education and the ability to self-administer acute medication. Having access to treatment eased patients' anxiety and improved their sense of

control and independence. Attacks were shorter when treated quickly, reducing the duration of their impact on HRQoL, and in some cases, caregivers were taught to administer the injection to the patient, which further reduced the patient's anxiety. Pre-procedural prophylaxis helped prevent attacks resulting from dental or medical procedures, and long-term prophylaxis typically reduced the frequency of attacks.

Attack-related resource utilization. Some participants reported that they self-injected their acute medication during attacks, while others routinely go to the hospital emergency department for their injection. The need to travel to the hospital or clinic for an injection was reported to be inconvenient. One participant mentioned that she often must wait until the next morning when her child is at daycare to go to the hospital for treatment if she is unable to find a babysitter, forcing her to endure long periods of pain. Attack-related costs were primarily related to medications and treatment visits, including co-payments and supplies, such as syringes and alcohol swabs, or travel expenses to the health centre, such as taxis, parking and fuel.

Caregiver impacts. Participants perceived that attacks have a substantial impact on their caregivers, who were primarily family and friends. This included an emotional burden of needing to be prepared to take their loved one for treatment

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if needed or to administer the injection. Concerns were also expressed about the need to take on additional responsibilities in the home while the patient is ill. Participants indicated that their caregivers had to miss work at times to accompany them to the hospital during severe attacks.

Long-term impacts. The impact of recurrent, unpredictable acute attacks had long-term implications for the participants, including psychosocial issues, career and educational setbacks, as well as impacts on long-term resource utilization. Table SIII¹ presents selected quotes referring to long-term impacts of HAE.

Psychosocial impacts. Participants experience long-term psychosocial impacts, including anxiety about having children, worry, and social/relationship impairment. Some chose not to have children or to have fewer children than desired, which caused emotional distress and may have contributed to marital problems. Many felt forced to avoid travelling, certain hobbies, or social opportunities, and consequently felt that their relationships suffered.

Career and educational impacts. Due to their anxiety about future attacks and the unpredictable nature of HAE, some participants felt that their career choices were limited or experienced setbacks in their career. Some felt that they could only work part-time, were unable to perform certain job tasks, or were unable to keep up with work due to frequent missed days. One participant reported that having HAE caused her to take much longer than expected to complete her education. Some perceived discrimination in the workplace or a lack of understanding or assistance from their co-workers. Participants feared that they would not be able to complete their work at times, and they could potentially lose their jobs.

Long-term resource utilization. Resource utilization between attacks included missed time from work for routine care visits, prescription co-payments for prophylaxis for HAE. This could occasionally include their children as well. Other costs included travel expenses, such as fuel, tolls and parking. Patients who take long-term oral prophylaxis therapy may experience bothersome side-effects, which may lead to discontinuation. In some cases, long-term prophylaxis was ineffective. Others worried about potential long-term consequences that the medication might have.

Adolescents/young adults. The 5 participants between the ages of 15 and 25 years identified some impacts found to be unique within this age group. In some cases, the adolescent/young adult had a parent with HAE, and therefore was diagnosed with HAE either before symptom onset or shortly thereafter. An early diagnosis prevented these patients undergoing any unnecessary treatment prior to diagnosis. Adolescents noted that having HAE impaired their participation in school activities and that they were unable to keep up with their peers: "Mostly, it limits my ability to do any physical sport...for example, during physical education class at school, I can't do all the same things as my classmates....I have to do a lot less physically." They expressed some anxiety about potentially not being able to achieve everything they would like to in the future given their diagnosis: "You think about having children, a family, an education. And one thinks that it wouldn't be possible to handle all this."

DISCUSSION

The findings from the qualitative research demonstrate the wide-ranging impact of HAE on a patient's life. Part of the HAE humanistic and economic burden has been described previously (15, 20, 21). HAE not only causes substantial short-term disability associated with attacks, but, in between attacks, patients may live in

persistent anxiety and disappointment, being prevented from participating in selected activities. As such, patients experience substantial psychosocial burden living day-to-day with HAE. The long-term effects of the disease on the patient's lifestyle, emotional health, career, educational attainment, family life and medical resource utilization have important and lasting effects, and may also affect caregivers' quality of life.

The conceptual model (see Fig. 1) provides a means of presenting and organizing these different ideas into a schema. The model allows us to understand the different ways that people's lives are affected in general by HAE (there may still of course be idiosyncratic impacts that go beyond the model). Based upon the qualitative work the conceptual model allows us to plan how patient-centred outcomes should be captured in clinical trials and other studies. The model could also be used to generate hypotheses and predictions, which could be subsequently tested. This indeed could help to refine the model.

This approach to understanding the wider burden of disease in HAE can find some parallels in the literature, which underline the usefulness of this methodology. Buchbinder et al. (22), for example, undertook a very similar exercise to understand the impact of low-back pain. This research mapped out the main impact of back pain, but also identified domains not previously considered, including loss of independence and worry about the future.

A strength of this study is that participants were chosen from 3 countries with different approaches to treatment, including varying availability of long-term prophylaxis medications. Despite several available treatments in 2011, the findings highlight an unmet need for more effective treatments of HAE attacks. This could help to alleviate patients' anxiety, reducing activity limitations, improving ability to participate in hobbies, and improving chances for long-term success in their careers and personal lives.

The interview participants were recruited non-systematically, subjecting the conceptual model results to potential selection bias. Demographic and clinical characteristics were highly consistent with the HAE-BOIS-Europe survey participants (15), suggesting that the interview participants were representative of the overall study population. Although we studied only 30 patients, the sample provided a rich source of data for identifying and characterizing the key impacts of living with HAE. Only 5 participants were aged 25 years or younger, which limited our ability to draw conclusions about their unique experience in comparison with older participants. Moreover, some of the categories in the conceptual model are overlapping. It would be useful to further substantiate the findings in this study and potentially develop clearer distinctions among the categories in future larger-scale quantitative modelling

studies. We recommend additional research to further explore the impact of HAE on young people in many more countries. The burden and impact of HAE may be very different where people do not have access to acute treatments.

In conclusion, it is not only the acute attack itself that affects the HAE patient's quality of life, but people with HAE experience long-term lifestyle modifications to accommodate their disease. In addition, caregivers often share the burden of HAE. The conceptual model highlights important issues for consideration in the clinical management of HAE patients. This model helps to advocate for patients and to improve support and services. The conceptual model should raise awareness of the patient's experience of HAE among policymakers and the healthcare community, and help to guide measurement of HRQoL outcomes in future evaluations of treatment effectiveness in HAE.

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