THE CURRENT STATE OF MANAGEMENT OF HAE IN EUROPE

HAEi

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Four years ago, HAEi (the international umbrella organization for the world's HAE patient groups) published our report, 'State of Management of HAE in Europe'. At that time, the majority of healthcare professionals had limited knowledge of hereditary angioedema (HAE), which resulted in under diagnosis, under treatment and little understanding of the disorder's impact on quality of life. Great disparity also existed in availability and access to treatment in countries across Europe.

There are now a number of HAE management and treatment guidelines as well as additional data on the burden of living with HAE. Nevertheless, disease recognition, treatment approval and reimbursement barriers remain high hurdles in many European countries, and the dream of consistent access to appropriate therapies remains challenging.

Overall, some progress has been made with the approval of additional modern HAE treatment options and clinical trials for promising next generation therapies.
However, basic access to life saving therapies still eludes patients in many European countries and unfortunately, our HAE patient call to action remains as salient now as it was in 2012. Clearly, more must be done to help HAE patients in Europe.

HAEi believes that broader access to modern therapies can reduce the pain, suffering and disability associated with this serious disorder, and dramatically increase quality of life.

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Chapter 1

Introduction

> "For me the worst thing is that most people, including physicians, do not understand me and do not understand the disease."

What is HAE? An overview

Hereditary angioedema (HAE) is a very rare and potentially life-threatening genetic condition that occurs in about 1 in 10,000 to 1 in 50,000 people.[1,2]

HAE symptoms include episodes of edema (swelling) in various body parts including the hands, feet, face and airway. In addition, patients often have bouts of excruciating abdominal pain, nausea and vomiting that is caused by swelling in the intestinal wall.[1,3] Airway swelling is particularly dangerous, and can lead to death by asphyxiation. Before therapy became available, the mortality rate for airway obstruction was reportedly as high as 30 percent.[2]

The episodes of swelling are unpredictable and the frequency varies dramatically among patients. Untreated, some patients experience attacks as little as once a year, around 30 percent of patients experience more than one attack per month and some patients have swelling episodes every week.[4,5,6] Most patients experience their first attack during childhood or adolescence.[5]

HAE patients have a defect in the gene that controls a blood protein called C1-inhibitor. The genetic defect results in production of either inadequate or non-functioning C1-inhibitor protein. Normal C1-inhibitor helps to regulate the complex biochemical interactions of blood-based systems involved in disease fighting, inflammatory response and coagulation.[6] Because defective C1-inhibitor does not adequately perform its regulatory function, a biochemical imbalance can occur and produce unwanted peptides that induce the capillaries to release fluids into surrounding tissue, thereby causing edema.[6]

In principle, HAE is simple to diagnose. In reality, as a rare disease, an accurate HAE diagnosis is often delayed for many years. HAE has symptoms that are similar to those of many other common conditions, resulting in frequent misdiagnosis. A large number of patients report to HAEi that their frequent and severe abdominal pain was inappropriately diagnosed as psychosomatic, resulting in referral for psychiatric evaluation. As the symptoms of the abdominal HAE swelling mimics appendicitis, unnecessary exploratory surgery has been performed on patients experiencing gastrointestinal edema. A person with HAE has often been through a long lasting ordeal by the time they receive an accurate diagnosis.

> "I have had my appendix removed, have been brushed in the throat with adrenalin, and have been on a 14 days diet consisting of nothing but bread made from rice and Tuborg beer – all just because the doctors couldn't find out what was wrong with me."

How do you get HAE? It runs in the family

HAE is so-called because the genetic defect that causes the swelling attacks is hereditary, meaning it is passed on in families. A child has a 50 percent chance of inheriting HAE if one of their parents has the disorder.[7]

The absence of family history does not rule out an HAE diagnosis. Up to 25 percent of HAE cases are due to a spontaneous mutation of the C1-inhibitor gene that occurs at conception.[5] People with HAE due to spontaneous gene mutation can then pass the defective gene to their offspring.

How is HAE diagnosed?

Most cases of angioedema turn out not to be HAE, because more commonly swelling attacks are:

- Allergic reactions - unlike HAE, allergic swelling attacks respond to antihistamines, corticosteroids or epinephrine and are also accompanied by hives[1]
- Swellings caused by something other than C1-inhibitor deficiency.

Assessing patient symptoms and reviewing family history are the most common first steps taken towards diagnosing HAE. Laboratory analysis of blood samples or genetic testing is required to establish an HAE diagnosis. Three blood parameter measurements are assessed to confirm HAE:[1,8]

- C4 levels
- C1-inhibitor level - quantitative (antigenic)
- C1-inhibitor level - functional

As most physicians may never see a patient with HAE, they are unlikely to recognize the symptoms, or may mistake HAE for something else. The average time between the onset of symptoms and diagnosis can range from 13-21 years.[7,9]

For people with HAE, it is critical to receive an accurate diagnosis as early in life as possible: the risk of death, mainly due to suffocation during an airway swelling, can be up to nine times higher in those with undiagnosed HAE compared to patients with a confirmed diagnosis.[10]

There are two main forms of HAE, as shown in table 1.[5] The most common form of the disease - Type I - is characterized by reduced levels/amounts of functional C1-inhibitor and affects about 85 percent of patients. Type II HAE affects about 15 percent of patients. In these patients, C1-inhibitor levels are normal or can be elevated, but the protein does not function properly. The two types are symptomatically identical. The two types are symptomatically identical and occur with roughly the same frequency in men and women.[5]

Several investigators have noted a familial (and therefore inherited) angioedema in patients with normal levels of C1-inhibitor. Now found under the designation of "HAE with normal C1 Inhibitor", this form of angioedema has very similar symptoms to HAE Type 1 and 2 and is yet to be fully understood.[8]

Table 1: Hereditary angioedema subtypes[5]

Type	Cause	Affects
Type 1	Low levels/amounts of C1-inhibitor C1-inhibitor functions properly Low C4 levels	Around 85 percent of cases
Type 2	Normal or raised levels of C1-Inhibitor C1-inhibitor does not function properly Low C4 levels	Around 15 percent of cases

What is happening when a HAE swelling attack occurs?

The genetic defect in HAE results in production of either reduced levels or non-functioning C1-inhibitor, a protein in the blood. When working normally, C1-inhibitor helps to regulate the complex biochemical interactions of blood based systems involved in fighting disease, inflammatory response and coagulation.[6] When there isn't enough C1-inhibitor, or it does not perform its regulatory function properly, a biochemical imbalance can occur and results in an excess of a peptide called bradykinin. Bradykinin induces the smallest of the body's blood vessels (capillaries) to release fluids into surrounding tissues, thereby causing swelling.[6]

What triggers an HAE attack?

Most swelling attacks occur spontaneously, with no apparent reason. However, anxiety, stress, minor trauma, surgery and illnesses such as colds and flu have been cited as triggers.[1] Patients have also reported swelling in extremities following physical activities for example a hand swelling following typing/prolonged writing, pushing a lawn mower or hammering or for example a foot swelling after gardening/digging with a spade or standing for a long time.[11] HAE patients are particularly vulnerable to airway attacks as a result of trauma to the oral cavity caused by dental procedures.[11]

In women, menstruation and pregnancy have been noted as having a major affect on disease activity. Use of oral contraceptives and hormone replacement therapy can be associated with an increase in the frequency and severity of attacks.[1]

ACE Inhibitors, often prescribed to treat high blood pressure, have been known to increase the frequency and intensity of HAE attacks.[1]

What does an HAE attack look and feel like?

HAE attacks are all different. Doctors and patients cannot predict the frequency, severity or location of attacks, even among patients within the same family. Untreated, an average attack can last 2-5 days,[12] but some attacks may go on for a week.[4] It is not uncommon for patients to experience HAE attacks in more than one location at the same time.

HAE attacks do not usually cause raised areas (wheals) or an itchy red rash (hives).

The following section includes patient pictures to show examples of different types of swelling attack. It is important to remember that no two patients are alike and no two attacks are alike.

Face and throat swelling

Swelling of the face can be disfiguring and extremely painful. Facial swelling can also lead to swelling in the throat.[13]

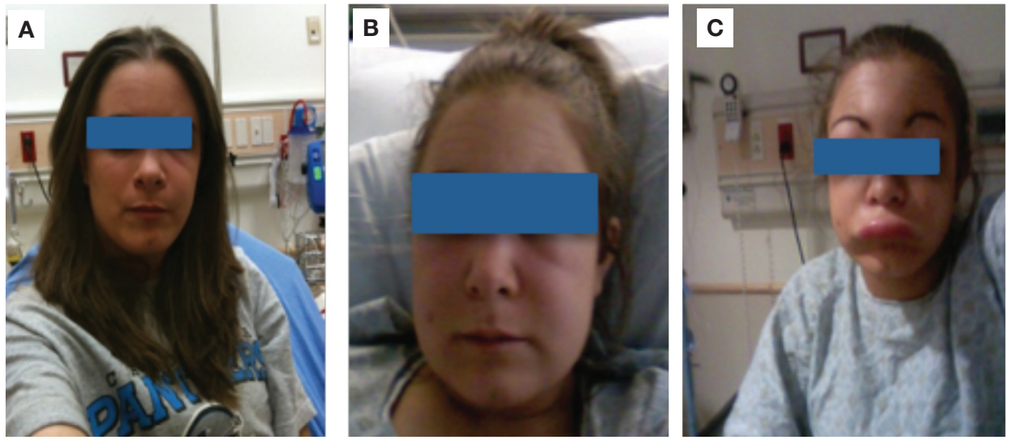

Figure 1: Progression of an HAE facial swelling from start of attack (A) to height of attack (C)

During a throat attack the airway can close, causing suffocation and in some cases, death. As a result, throat attacks must be treated as an emergency, and patients must seek prompt medical attention. Studies indicate that more than 50 percent of patients will endure at least one throat attack in their lifetime.[13]

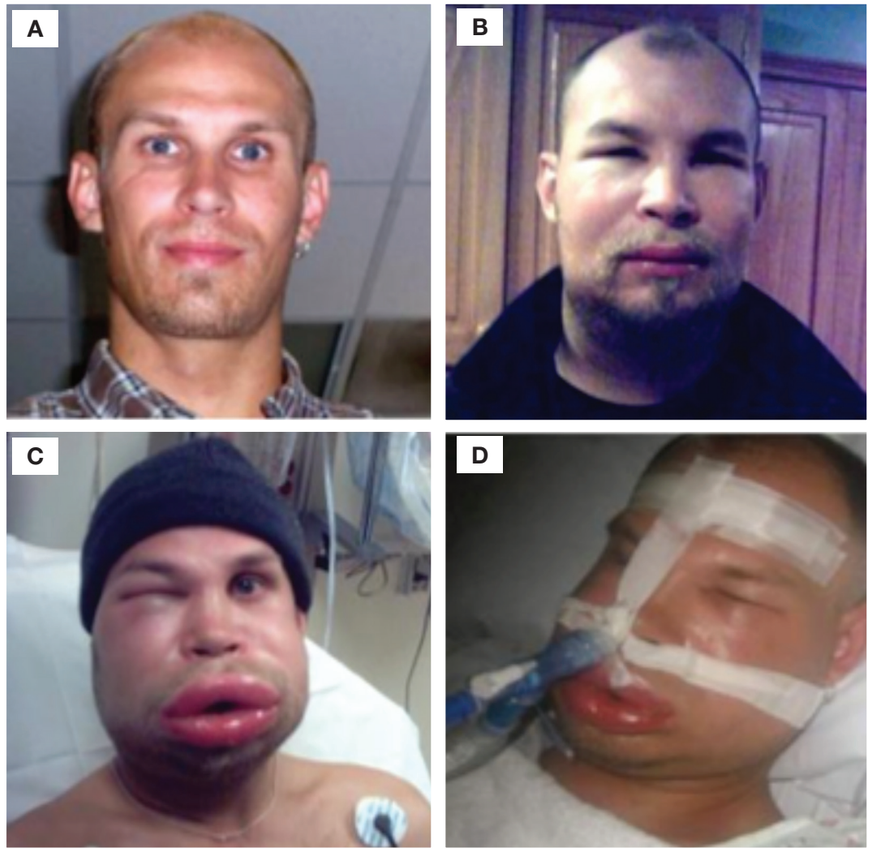

Figure 2: Progression of a laryngeal attack from pre-attack (A) to intubation (D)

"My grandfather had severe HAE over many years and he died from a throat swelling at the age of 39, leaving four children, three of whom had HAE. My father suffered much until he was 30, when his symptoms suddenly ceased, never to return. Although many members of the family had the condition, my mother regarded it as 'all down to nerves' and 'all in the mind'."

Abdominal swelling

Abdominal attacks are one of the most common type of HAE attack[1,3,7] and almost all HAE patients will experience them. Abdominal swelling involves pain (which can be excruciating), vomiting and diarrhea.[3] These types of attacks mimic abdominal emergencies and are often misdiagnosed, resulting in exploratory procedures or unnecessary emergency surgery (e.g. appendicitis).[5] Around one third of HAE patients will have their abdominal attack symptoms misdiagnosed and undergo unnecessary surgery.[14]

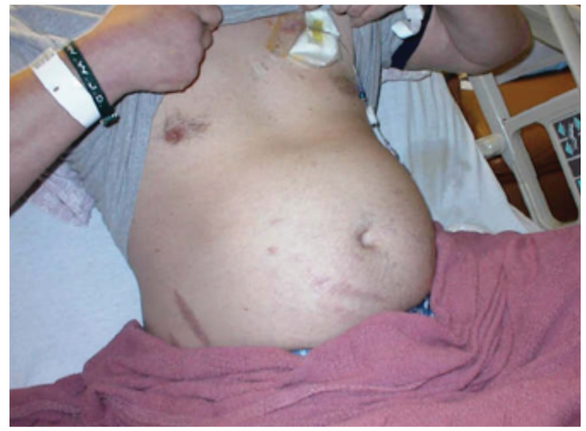

Figure 3: Male with an abdominal HAE swelling

Abdominal pain is rarely seen in other types of angioedema.

Hand and feet (extremities) swelling

Swelling of the hands and feet can prevent people from doing everyday tasks such as writing, driving, walking or even standing. Extremity or peripheral swelling attacks can happen in a single location (e.g. left foot) or multiple locations at the same time (e.g. left foot and right hand). As with all swelling attacks, extremity attacks are also debilitating and painful.

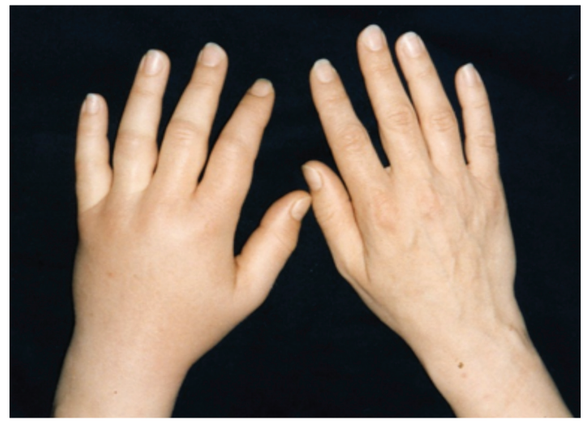

Figure 4: Swelling to the left hand due to an HAE attack in that location

How is HAE treated?

Treatment options for HAE patients have evolved significantly. Modern therapies offer marked benefits for patients, including significant improvements in quality of life due to the improved management of attacks. The ongoing challenge for HAE patients is to secure consistent access to these life saving therapies. (Table 2)

There are two goals for HAE therapies; either to treat attacks once they have begun (acute therapy) or to prevent attacks from occurring (prophylaxis or prevention therapy).

There are some cases where therapies are used specifically to mitigate the risk of an attack occurring for example before a dental or medical/surgical intervention (pre-procedure therapy).

Table 2: Therapies licensed in Europe specifically for the management of HAE

Brand name (generic name)	Class of drug	Administered
Acute treatment		
Berinert	C1-inhibitor concentrate (human plasma derived)	Intravenous infusion
Cinryze	C1-inhibitor concentrate (human plasma derived)	Intravenous infusion
Firazyr (icatibant)	B2 bradykinin receptor antagonist	Subcutaneous injection
Ruconest (conestat alfa)	Recombinant C-1 inhibitor (not human plasma derived)	Intravenous infusion
Prophylaxis: pre-procedure prevention of attacks		
Berinert	C1-inhibitor concentrate (human plasma derived)	Intravenous infusion
Cinryze	C1-inhibitor concentrate (human plasma derived)	Intravenous infusion
Prophylaxis: long-term prevention of attacks		
Cinryze	C1-inhibitor concentrate (human plasma derived)	Intravenous infusion

From ema.europa.eu and mri.medagencies.org
Accessed November 2015

Other older therapies used in the absence of modern therapies. These may not have a specific license or data to support use in HAE:

Generic name	Class of drug	Administered
Acute treatment		
Fresh frozen plasma	Fresh frozen plasma	Intravenous infusion
Prophylaxis (prevention of attacks)		
Danazol, stanozolol, oxandrolone	Anabolic steroid (or other attenuated androgens)	Oral
Tranexamic acid	Antifibrinolytic	Oral

Intravenous = in the vein
Subcutaneous = under the skin
Oral = pill

While anabolic steroids/androgens have been shown to be useful, the medicines are (1) linked to liver toxicity,[15] (2) associated with an increase in cholesterol levels[16] and (3) as anabolic steroids are male hormones, their side effects can be particularly severe in female patients. In addition these drugs should not be used in children or women who are pregnant or breastfeeding.[15,16]

Chapter 2

New Insights into the Reality of Living with HAE

The first State of Management of HAE in Europe report described the substantial burden of HAE and impact of missed days of work, school and leisure activities on a patient's quality of life. Because a typical, untreated, attack usually lasts several days before it subsides, people with HAE may experience symptoms for over three months a year.[17] People with HAE suffer from decreased physical and mental health, including depression and HAE can cause patients to withdraw from education, work and social activities.[16] Since the first report was issued, additional data has been published which corroborates many of these findings. This includes the HAE European Burden of Illness Study (HAE-BOIS) referred to in this section.

All attacks mean swelling; swelling means pain

In the recent HAE-BOIS (n=164), all respondents reported pain associated with their most recent swelling attack. Two thirds of respondents rated the pain (and swelling) as either 'moderate' or 'severe'.[18]

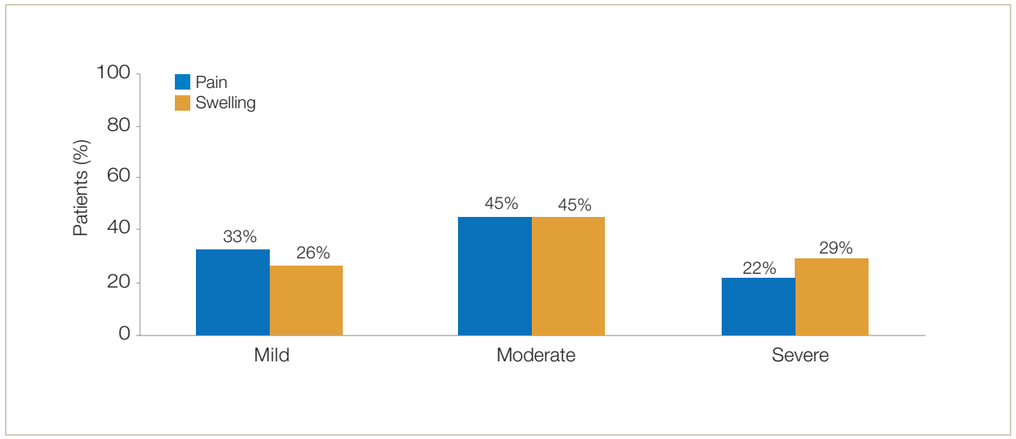

Figure 5: Distribution of patients by rating of pain and swelling severity of their last attack (n=164)

Pain impacts life; swelling attacks reduce ability to carry out daily activities and result in missed days at work/school

The more pain a person experienced as a result of their swelling attack, the higher the impact on their ability to work, go to school, or carry out usual daily activities.[18]

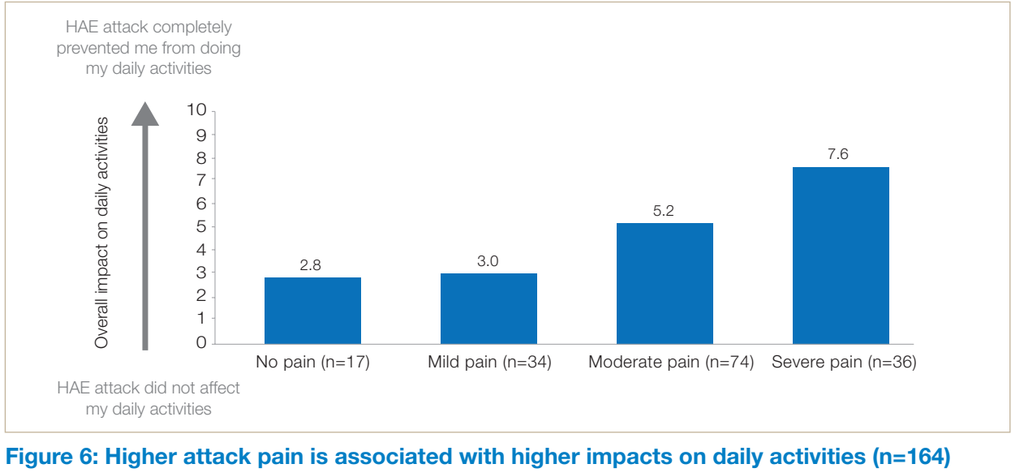

Figure 6: Higher attack pain is associated with higher impacts on daily activities (n=164)

The pain experienced during a swelling attack is associated with decreased productivity and absenteeism from school/work.[19]

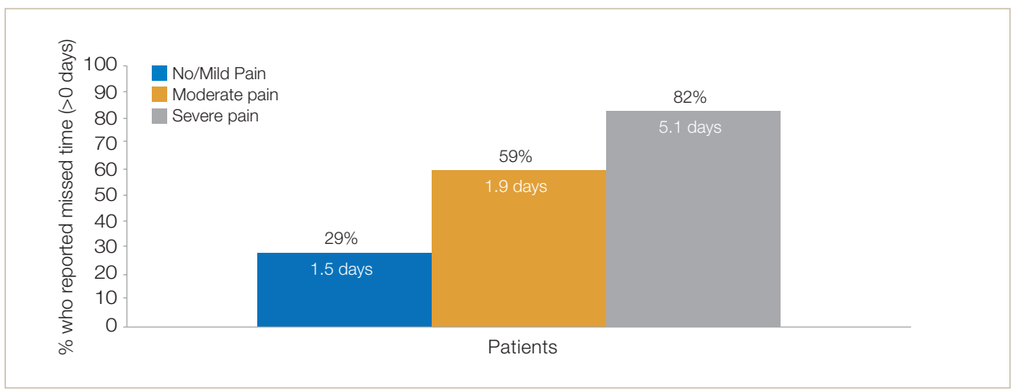

Figure 7: Work/school absenteeism during last attack by pain severity. Percentage who missed time and reported mean days missed. Percentage based on 72 patients who were employed or in school and provided absenteeism data.

All attacks impact life, regardless of their location

A traditional or general assumption is that extremity swelling is painless,[20] not considered severe and therefore treatment for these attacks is often less necessary.[18] However, another separate study indicates that these attacks present serious clinical impact.

In a recent European and North American study (n=64), over half of patients reported that one extremity HAE attack involved multiple swelling sites.[20] More than 80 percent of the patients who experienced a severe extremity attack reported moderate to severe dysfunction and pain of the affected site.[20]

When considering attack location and impact on time lost from daily activities, the HAE-BOIS study found that the impact on time prevented from daily activities did not vary significantly across attack location. (Figure 8)

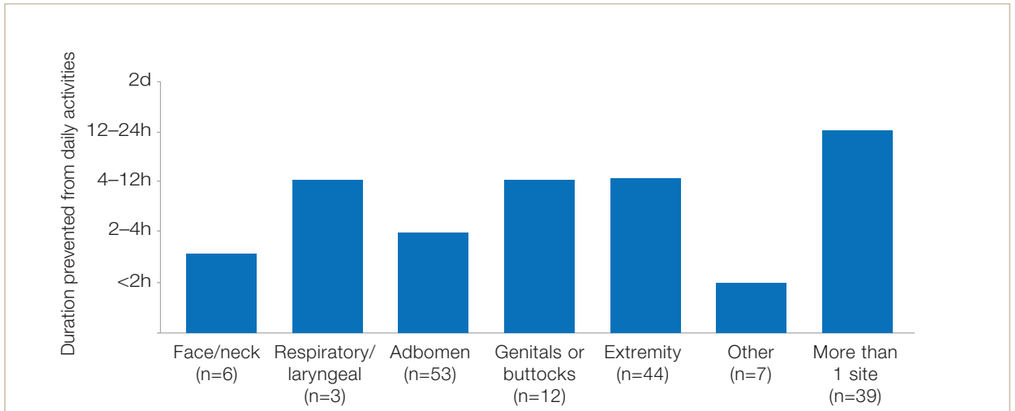

Figure 8: Median duration prevented from daily activities by attack location (n=164)

The impact of HAE goes beyond the individual and the attack

Even when HAE patients are not having an attack, many can experience anxiety, which can limit daily activities.[18] This is comparable to other chronic conditions, such as migraine headaches, that typically involve "acute" (severe and sudden onset) events. People with HAE also report substantial anxiety about passing HAE to their children, future attacks and travelling.[18]

Like other chronic diseases, the impact of HAE goes beyond the individual and affects the entire family. Caregivers; whether family members, partners or friends, may have to take time out of their usual activities, including work, to care for a person who is having an HAE attack. People with HAE often report that their spouse has to 'take over' household duties and childcare when they are debilitated by an attack.

> "I can only sit down in my chair and just stare. And then my wife has to do all the work at home on her own, because I cannot take my share."

Attack pain severity is an important predictor of socioeconomic impact with more severe pain having greater impact and disruption on patients and their caregivers.[19] (Figure 9)

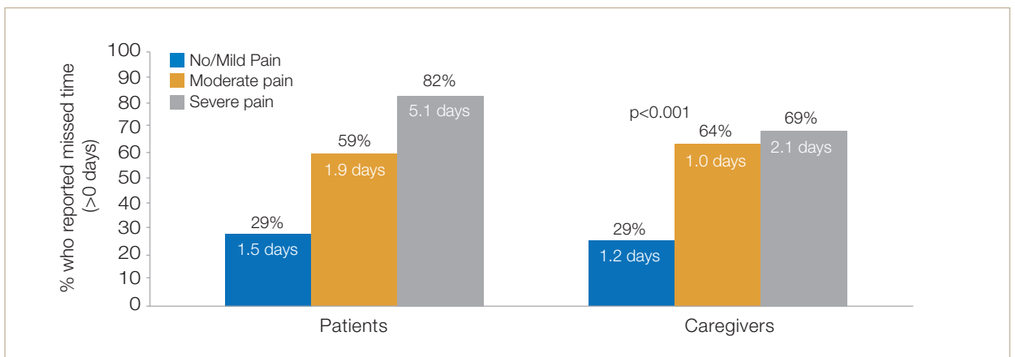

Figure 9: Work/school absenteeism during last attack by pain severity. Percentage who missed time and reported mean days missed. (a) p-values for difference in percentage who missed time. Percentage based on 72 patients who were employed or in school and provided absenteeism data. Percentage of caregivers based on full sample (N=164). Note: Means based on number of patients (n=40) and caregivers (n=86) who missed time. Caregiver time includes leisure time. Data missing for 31 caregivers.

Why wouldn't you treat an attack?

The fact that (1) HAE attacks are painful and debilitating, and (2) the time prevented from daily activities does not vary significantly by affected body site, suggests that all attacks have a negative impact on a patient's life. However, the HAE-BOIS study revealed that only attacks in potentially life threatening locations (respiratory/laryngeal and face/neck) were treated in 100 percent of the cases.*

Discussions with patients from HAEi member organizations suggest the disparity in treating attacks depending on their location can be linked to limited access to treatment. For example, modern therapy is provided in limited quantities and for specific life-threatening attacks only, or there is the fear that treatment will be revoked if 'too much' is used or used for attacks perceived to be in less severe locations.

These underlying questions/fears result in patients being selective in which attacks they treat. This does not fit with the principles of a modern approach to the management of HAE.

> "When I get an abdominal attack, I have to stop my daily activities especially if I'm vomiting or bent over from pain or if I need someone to help me… When I get swollen feet, I can't do anything because the bottom of the foot is swollen and the toes. And if your hands get swollen, you also can't do much either. When my hands swell up, I can't even tie my shoes."

*HAE-BOIS data on file

Chapter 3

HAE Modern Management Principles

Recent international guidelines and consensus frameworks advocate a modern approach to HAE management.[8,15] HAEi endorses the basic principles established in these documents. Consistent with the recommendations, where modern HAE medication is available, HAEi believes patients should be able to expect:

1. **To live as normal a life as possible via an optimal individualized treatment plan**
   - HAE can be successfully managed when patients can access and use HAE modern therapies to treat attacks
   - The choice of modern HAE treatment should be a joint decision between patient and physician
   - Access to the modern HAE treatment should be consistent and continuous
   - Family members of patients with HAE should be screened so that appropriate therapy can be available for treatment, especially because the first event may be of the upper airway and fatal without appropriate therapy

2. **To self-treat attacks as early as possible, as all attacks are debilitating and airway attacks could be life-threatening**
   - HAE patients should always have modern HAE therapy available to treat an acute attack
   - Two 'attack' doses of acute therapy should be made available to a patient for use "on demand"
   - Patients should be trained in self-administration
   - All attacks should be considered eligible for treatment when a patient recognizes HAE swelling
   - Attacks occurring in any location can be treated at home. In the case of a laryngeal attack, patients should seek expert medical advice in the ER even if self-treated at home

3. **To be assessed for long-term preventive therapy where appropriate**
    - In general, prophylactic treatment should be considered when on-demand acute treatment is inadequate to minimize the suffering related to HAE
    - When assessing appropriate use of long-term prevention, factors to consider include how attacks impact patient quality of life, other health problems and patient preferences
    - Short-term prophylaxis should be considered before surgeries, especially dental or procedures where the airways are manipulated (e.g. endoscopy) due to the risk of swelling in these areas

4. **Use of modern HAE medications will be prioritized vs. older out-dated medications**
    - The use of androgens should be avoided when contraindicated, where patients are concerned about or have risk factors for adverse events, when poorly tolerated or with poor response or when high doses are required
    - There should be no pre-requisite to 'fail' androgen therapy before considering other prophylactic treatment
    - Where androgens are prescribed, patients should be routinely monitored for adverse events
    - Oral antifibrinolytics (e.g. tranexamic acid) and oral steroids (e.g. danzaol), are not to be used as on-demand treatment

Chapter 4

The European Call to Action

There is still much to do to ensure that all HAE patients in Europe have access to modern HAE therapy, so that they can control their symptoms, feel safe, and fulfill their life's potential at school, work, and in their relationships.

Patients throughout Europe still call for:

- Governments, health authorities and health professionals to recognize that HAE is a serious disabling, potentially life-threatening and chronic condition that must receive timely, accurate diagnosis and effective treatment.
- Professional education that enables health professionals to recognize HAE symptoms, diagnose the condition, and appropriately treat attacks, and understand the importance of specialist referral and ongoing care.
- Public and patient education that increases HAE awareness, and encourages patients to;
    - Seek information on currently available treatment options
    - Form a partnership with their HAE treating physician
- A treatment plan that meets each patient's individual needs considers home treatment as a viable option and follows the HAE Modern Management Principles.
- Co-operation among stakeholders – patients, scientists, specialist doctors and industry – to continue research, including clinical trials, to improve treatment and ultimately to find a cure for HAE.
- Co-operation among national governments, regulatory authorities and industry to ensure continuing and where appropriate, improved access to available treatments.

Chapter 5

HAEi: Advocating on Behalf of Patients

HAEi is the international umbrella organization for the world's HAE patient organisations. HAEi is dedicated to raising awareness of C1-inhibitor deficiencies around the world.

Every day we have HAE friends from all over the world joining the HAEi family. Through the HAEi newsletter, people can keep up to date on everything relevant to HAE and via our social media channels such as Facebook, share stories, ask questions and support others within the HAEi family. HAEi organizes the annual global HAE awareness day, **hae day :-)** with the theme "many faces, one family" and holds a global patient conference every other year.

HAEi strives to improve time to diagnosis and facilitate access to and reimbursement of life saving HAE therapies, which will enable lifelong health for all patients – no matter where they live.

HAEi is intensely aware of the significant unmet medical need in countries where limited or no HAE medications are available. As part of HAEi's work to increase access to medicines, we initiated HAEi Global Access Program (HAEi GAP). The HAEi GAP model initially includes a 'Named Patient Program' where governments/hospitals order the medicine and provide reimbursement. Later it is also planned to include an 'Early Access Program' where access to medication will be given in conjunction with a phase III clinical trial, and a 'Compassionate Use Program' that offers donated medication to patients in parts of the world where this type of program is allowed.

For more information on the work of HAEi and the HAE patient support groups that exist across the world, please see our website: www.haei.org

Disclaimer

References

1. Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol. 2004 Sep;114(3 Suppl):S51-131
2. Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol. 2008 Jan;100(1 Suppl 2):S30-40
3. Bork K, Stauback P, Eckardt AJ, et al. Symptoms, course and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. Am J Gastroenterol. 2006 Mar;101(3):619-27
4. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. Br J Dermatol. 2009 Nov;161(5):1153-8
5. Zuraw BL. Clinical Practice. Hereditary angioedema. N Engl J Med. 2008 Sep 4;359(10):1027-36
6. Davis AE. New treatments addressing the pathophysiology of hereditary Angioedema. Clin Mol Allergy. 2008 Apr 14;6:2
7. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. Ann Intern Med. 1976 May;84(5):580-93
8. Craig T, Aygoren-Pursun E, Bork K, et al. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 2012 Dec;5(12):182-99
9. Roche O, Blanch A, Caballero T, et al. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol. 2005 Apr;94(4):498-503
10. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol. 2012 Sep;130(3):692-7
11. 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 Sep-Oct;1(5):458-67
12. Riedl MA. Creating a comprehensive treatment plan for hereditary angioedema. Immunol Allergy Clin North Am. 2013 Nov;33(4):471-85
13. 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 May 26;163(10): 1229-35
14. Agostini A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine (Baltimore). 1992 Jul;71(4):206-15
15. Cicardi M, Bork K, Caballero T, 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 Feb;67(2):147-57
16. 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 Sep-Oct;31(5):407-14
17. Cicardi M, Agostini A. Hereditary angioedema. N Engl J Med. 1996 Jun 20;334(25):1666-7
18. Caballero T, Aygören-Pürsün EBK, Hautamaki E, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. Allergy Asthma Proc. 2014 Jan-Feb;35(1):47-53
19. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema:results from the hereditary angioedema burden of illness study in Europe. Orphanet J Rare Dis. 2014 Jul 4;9:99
20. Kusuma A, Relan A, Knulst AC, et al. Clinical Impact of Peripheral Attacks in Hereditary Angioedema Patients. Am J Med. 2012 Sep;125(9):937.e17-24

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