

CLINICAL REPORT

Hereditary Angioedema in Swedish Adults: Report From the National Cohort

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Hereditary angioedema (HAE) is rare, disabling and sometimes life-threatening. The aim of this study is to describe its prevalence, symptomatology and treatment in Sweden. A total of 146 patients were identified; 110 adults and 36 children with HAE type I ($n=136$) or II ($n=10$), giving a minimum HAE prevalence of 1.54/100,000. All patients received a written questionnaire followed by a structured telephone interview. This report focuses on the 102 adults who responded. Females reported 19 attacks in the previous year vs. 9 for males ($p<0.01$), and females reported 10 days of sick leave vs. 4 days for males ($p<0.05$). For all treated acute attacks, plasma-derived C1-inhibitor concentrate (pdC1INH) (used in 27% of patients) had a good effect. For maintenance treatment, 43% used attenuated androgens and 8% used pdC1INH, which reduced their attack rate by more than 50%. In conclusion, the minimum HAE prevalence in Sweden was 1.54/100,000. HAE affected females more severely. Attenuated androgens and pdC1INH had a good effect on preventing attacks. *Key words: C1-inhibitor deficiency; census; clinical manifestations; epidemiology; hereditary angioedema; prevalence; Sweden.*

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There are two types of hereditary angioedema (HAE) due to C1-inhibitor (C1INH) deficiency: type I with a low amount of C1INH, and type II with normal or high level of faulty C1INH with low function (1). In recent years, another form of HAE with similar clinical manifestations has been found called either HAE with normal C1INH, or HAE type III (2). Some cases of HAE type III have been associated with a mutation of the gene for Factor XII (3). This type has not yet been diagnosed in Sweden (Thomas Renné, Karolinska Institutet, personal communication). In all types of HAE the main mediator is thought to be bradykinin (4).

The prevalence of HAE is reported to be approximately 2/100,000 (5–7). As HAE types I and II are

autosomal-dominant they affect just as many males as females. In up to 25% of patients, there is no family history of HAE, i.e. these patients have a new mutation (8).

HAE is characterized by attacks of angioedema in subcutaneous tissue and mucous membranes, and can affect many parts of the body. When angioedema appears in the tongue or larynx it can be life-threatening. If angioedema is located in the intestine it may cause severe abdominal pain and hypotension. Angioedema in other locations, such as the genitals, face, hands and feet, induces discomfort, and may impair daily activities. Untreated, an attack can last up to 5 days. Between attacks patients usually have no symptoms (9–11). Females often have a more severe disease than males, probably due to different hormonal activity (11).

HAE often implies increased sick leave and impaired health-related quality of life (HRQoL) both during and between attacks (12–16). The patients' sick-leave, recurrent visits to hospitals and expensive medications also place an economic burden on society (16, 17).

The prevalence and clinical data for subjects with HAE have not been studied in Sweden. Therefore, we initiated Sweha-Reg, a population-based national registry of HAE in Sweden with the objectives of providing epidemiological and clinical data (18). The aim of this study was to present data from Sweha-Reg, focusing on the prevalence of HAE types I and II in Sweden, and on the clinical manifestations and treatment in adults.

MATERIALS AND METHODS

Recruitment of patients

The Swedish national registry of patients with HAE, Sweha-Reg, has been described previously (18). In short, criteria for inclusion in the registry were willingness to participate and physician's diagnosis of HAE, including laboratory confirmation of either HAE type I or II (antigenic concentrations of C1INH <50% of normal values and/or functional levels of C1 inhibitor <50% (chromogenic assay) or <84% enzyme-linked immunoassay (ELISA) of normal values obtained after the first year of life) (19). We attempted to find all subjects in Sweden diagnosed with HAE, with the help of the Swedish Patient Organization (PIO) and by contacting the 2 special laboratories for complement deficiency analysis and all Swedish departments of internal medicine, otorhinolaryngology, allergology, dermatology and paediatrics. A total of 629 clinical units were approached, of whom 239 responded.

A total of 200 clinical units denied knowledge of any patients with HAE. After informed consent was obtained, the patients were recruited and consecutively entered into the registry. This report includes patients entered between 2007 and 2011.

Ethics

The study was approved by the regional ethics committee in Stockholm/Karolinska Institutet (Dnr2006/1467-31/2) and conforms to the principles of the Declaration of Helsinki. The Swedish Data Inspection Board approved the collection of individual data into a computerized register. All data were anonymized before statistical analysis.

Questionnaires

All patients were invited to participate in the study, and to answer a written questionnaire and then participate in a telephone interview. There was one questionnaire for children (0–17) and one for adults (≥ 18 years of age) (18). The patients (or the parents of children) who answered and returned the written questionnaire were telephoned for a 1-h structured interview performed by the same investigator (PN). Questionnaires covered demographic data, family history, and detailed clinical information on HAE.

Statistical analysis

Statistica 12 Software (Statsoft, Inc, Tulsa, Oklahoma, USA) was used for statistical analysis. The Mann-Whitney *U* test was used to analyse differences between groups for continuous variables. *p*-values < 0.05 were considered statistically significant. Descriptive results were presented as numbers, percentages, means, medians, and ranges, where appropriate.

RESULTS

Demographics, hereditary angioedema type and family history

A total of 142 patients with HAE were registered in the database of Sweha-Reg up to June 1, 2011, and we also knew of 4 other patients with HAE, who clearly stated that they did not want to participate in the questionnaires, giving a total of 146 known patients with HAE in Sweden. This gives a calculated minimum HAE type I/II prevalence of 1.54/100,000 in Sweden. All counties had patients with HAE. The patients' median age at entry to the study was 40 years, ranging between 1 and 87 years (Table I). Of the 142 patients in Sweha-Reg, 133 (94%) returned the written questionnaire and, of those, 129 participated in the telephone interview; a complete response rate of 91%.

Table I. Number of subjects with hereditary angioedema identified in Sweden, and numbers responding to the written patient questionnaire and the telephone interview by the physician

Base	All (F/M)	Children		Adults	
		0–17 years	Adults	(≥ 18 years)	(F/M)
Census	146 (71/75)	36 (16/20)	110 (55/55)		
Patient questionnaire	133 (63/70)	31 (13/18)	102 (50/52)		
Physician's telephone interview	128 (61/67)	29 (13/16)	99 (48/51)		

Including the 4 patients who did not want to be entered into Sweha-Reg, there were 136 patients with HAE type I and 10 with HAE type II. We were able to identify 39 families with up to 4 members affected, 36 with type I and 3 with type II. A total of 116 of the 133 responders of the written questionnaire (87%) were aware of at least one ancestor with HAE.

We present here the results for the 102 adults who answered the written questionnaire and the 99 adults who also participated in the telephone interview (Table I). Data from the children will be presented elsewhere.

Age at onset and at diagnosis among adults

The median age at onset of symptoms ($n=98$) was 12 years of age, ranging from 0 to 50 years; for females it was 13 years (range 1–50 years, $n=48$) and for males it was 10.5 years (range 0–50 years, $n=50$). The median age at diagnosis ($n=99$) was 22 years (range 1–81 years); for females it was 20.5 years (range 4–60 years, $n=48$) and for males it was 22 years (range 1–81 years, $n=51$). The median time duration to diagnosis for all those with onset of symptoms before diagnosis ($n=91$) was 10 years (range 0–67 years); for females it was 6 years (range 0–42 years, $n=45$) and for males it was 14 years (range 0–67 years, $n=46$). Eight subjects were biochemically diagnosed before onset of symptoms.

Clinical manifestations among adults

During the previous year, 20 patients had had no attacks and 80 had had attacks of angioedema ($n=100$). Of those who had had attacks we received data on attack frequency from 76 patients, who reported a median of 14 attacks. Females had approximately twice as many attacks in the previous year as males (19, range 2–165 attacks with the exception of 1 outlier with 475 attacks, vs. 9, range 1–42 attacks, $p < 0.01$). Since the start of HAE symptoms ($n=99$), 9% had experienced less than 1 attack, 15% 1–5 attacks, 28% 6–11 attacks, 36% 12–24 attacks and 11% had had more than 24 attacks yearly. Since the onset of HAE symptoms, 82% reported attacks usually in the skin, 78% in the abdomen, 27% in the larynx, 26% in the urogenital area, 20% in the lips, and 6% in the tongue ($n=98$).

The HAE attack frequency was defined as severe if the patient had experienced 12 or more attacks during the last 12 months, moderate 4–11 attacks, mild 1–3 attacks, and asymptomatic no attacks. During the previous 12 months, 47% of subjects had severe, 21% had moderate, and 11% had mild HAE-attack frequency, while 22% were asymptomatic ($n=96$). Four patients who stated they had angioedema were excluded because of missing data from the written questionnaire.

When patients were asked about the worst attack frequency during their lifetime, 40% had had a mean of 2.8 attacks per week, 45% 3.9 attacks per month, and

15% 4.0 attacks per year ($n=94$). Furthermore, when attacks were at their worst, 3% had an attack duration shorter than 12 h, 9% 12–24 h, 3% 1–2 days, 72% 2–5 days, and 12% longer than 5 days ($n=97$).

Irrespective of location, 65% of patients reported severe pain, 11% moderate, 9% mild and 13% no pain in association with HAE attacks ($n=96$). In addition, 5% had perceived severe, 13% moderate, and 24% mild itch, whereas 57% had no itch during attacks ($n=97$).

Concerning redness in areas with skin angioedema, 17% of patients always had redness, 47% had it sometimes and 36% never had it ($n=71$). Only those who had experienced angioedema in the previous year answered this question.

Prodromes were experienced by 68% ($n=98$). Of these patients, 27% reported tiredness, 24% physical sensations such as paraesthesia and/or pain, 22% altered mental state (e.g. anxiety, moodiness, depression), 21% rash, 9% abdominal sensations, 7% increased appetite and 4% nausea. Twenty-one percent reported more than one type of prodrome.

Trigger factors

Ninety-four of 99 patients (95%) were aware of trigger factors that provoked HAE attacks. Triggers were trauma (in 56%), mental stress (55%), infection (35%), physical exertion (13%), alcohol (4%), cold condition (3%) and menstruation (in 33% of women). Attacks with no obvious trigger were experienced by 62%.

Healthcare visits and sick leave

Since onset of symptoms, females reported a median of 15 healthcare visits (range 0–100, $n=48$) and males 10 (range 0–500, $n=51$) due to HAE. Females were reportedly hospitalized a median of 3 times (range 0–60, $n=46$) and males twice (range 0–100, $n=50$) because of HAE manifestations since the onset of HAE attacks. During the previous year, the median number of days on sick leave was significantly higher in females than in males (10, range 0–183, $n=37$ vs. 4, range 0–365, $n=35$; $p<0.05$).

Treatment

Patients were asked about treatment of acute attacks. They also graded the treatment effect as none, poor,

Table II. Proportion of subjects (%) reporting certain treatments for acute attacks ($n=98$). The median overall treatment effect was rated on a 4-step scale (no=0, poor=1, moderate=2 and very good effect=3)

Treatment	Skin		Abdomen		Larynx		Urogenital	
	%	Effect	%	Effect	%	Effect	%	Effect
PdC1INH	13	3	20	3	27	3	1	2
Fresh-frozen plasma	8	1	6	2	8	0	0	–
Tranexamic acid	13	1	8	1	16	0	0	–
Androgens	4	1	1	0	0	–	0	–
Intubation	0	–	0	–	6	3	0	–
Opioids	0	–	10	2	0	–	0	–
Epinephrine	12	1	5	2	27	1	0	–
NSAIDs	0	–	9	2	0	–	0	–
Diuretics	1	0	3	2	0	–	0	–
Glucocorticoids	18	1	6	0	25	0	1	2
Antihistamines	9	1	1	0	14	0	0	–
Others	5	1	10	0	3	1	0	–

PdC1INH: plasma derived C1-inhibitor; NSAIDs: non-steroidal anti-inflammatory drugs.

moderate or very good (Table II). Plasma-derived C1-inhibitor concentrate (pdC1INH) had been used in 27% of the patients for on-demand treatment of all locations of attacks with very good effect. Eight percent had been treated with fresh-frozen blood plasma with a moderate effect on abdominal attacks and with no effect on laryngeal attacks. Tranexamic acid had been used as an acute treatment in 16% with a poor effect on skin swellings and no effect on abdominal or laryngeal attacks. Androgens had at best a poor-to-moderate effect when used in 2% of patients on acute skin attacks. Other acute treatments were epinephrine, antihistamines, glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids (see Table II).

Eighty-eight patients had used maintenance treatment at some time during their lives, in the form of anti-fibrinolytics (49%), androgens (43%) and/or pdC1INH (8%). Anti-fibrinolytics had no preventive effect on attack frequency, while, in general, androgens and pdC1INH reduced the annual attack frequency by more than 50%. At the time of answering the questionnaire, 22 of the 88 patients (25%) were on androgens and 2 had previously used androgens. Fourteen had experienced side-effects, 9 females and 5 males. The side-effects were: weight gain ($n=9$), altered menstruation ($n=4$), acne ($n=3$), virilization ($n=2$), hyperlipidaemia ($n=1$), hypertension ($n=1$) and tiredness ($n=1$). Seven repor-

Table III. Reported influence of various factors on hereditary angioedema (HAE) symptoms in females. Symptoms are graded in 3 steps, from worse, no change to improved. "No HAE symptoms yet" means that the HAE was not yet symptomatic. Type values in bold ($n=50$)

Event	Worse, %	No change, %	Improved, %	Not answered, %	No HAE symptoms yet, %
Year of menarche ($n=50$)	30	22	0	0	48
Oestrogen contraception ($n=32$)	66	22	0	6	6
Gestagen contraception ($n=23$)	13	70	9	0	9
IUD contraception ($n=31$)	10	65	6	16	3
Pregnancy ($n=42$) ^a	55	14	24	0	7
Menopause ($n=15$)	0	60	40	0	0

^aOne female, who was worse during one pregnancy and better during another, was excluded.

ted more than one side-effect. No patients reported any major cardiovascular event, such as myocardial infarction or stroke in relation to androgen therapy.

Reproductive health among females

The influence of menarche, contraception, pregnancy and menopause on HAE symptoms is summarized in Table III.

During labour, 5 of 43 females who had been pregnant had complications; fever ($n=1$), bleeding ($n=1$), difficulty delivering the placenta ($n=1$), urinary tract infection ($n=1$), and an HAE attack ($n=1$).

Caesarean sections were made in 9 of the 43 patients, for the following reasons: due to stress of the foetus ($n=4$), delivery-related complications ($n=2$), HAE ($n=2$), planned ($n=1$), and reason unknown to patient ($n=1$). Twelve females had experienced miscarriages. In 2 cases, the foetuses were growth-retarded, and in 1 case intra-uterine death of the foetus occurred, and in another case the pregnancy was ectopic. The cause of miscarriage was unknown in the remaining 8 cases.

DISCUSSION

We registered a minimum prevalence of HAE in Sweden of 1.54/100,000, which is comparable with other European studies, e.g. 1.09/100,000 in Spain, 1.41/100,000 in Denmark and 1.54/100,000 in Italy (5–7). Other studies, e.g. from Taiwan, Japan or Brazil, have included too few patients in comparison with the number of inhabitants in their countries, thus these reports cannot be used for comparison (20–22). Type I HAE was much more prevalent than type II (93% vs. 7%), which is in line with a Danish report (5). Elsewhere, type I represents 85% of patients with HAE, so it seems that the pattern in Scandinavia is slightly different (1, 5, 7), probably due to background genetics.

The Swedish adults had a median diagnostic delay of 10 years. To compare with other studies we also calculated the mean diagnostic delay. In Bygum's study (5) it was 16.3 years for the whole Danish cohort, and the more recently diagnosed patients in Denmark had a diagnostic delay of 10.3 years. In comparison, the mean diagnostic time in our study was 12.3 years. Zanichelli et al. (23) studied 150 HAE patients from 6 European countries and found an overall median diagnostic delay of 8.5 years, with the shortest delay in Germany and the longest in Italy (2 vs. 15 years). The diagnostic delay in Sweden is still not acceptable, but is comparable to the rest of Europe. Diagnostic delay can be due to the rareness of the disease or to symptoms being mistaken for other more common diseases, such as histaminergic angioedema and acute abdominal illnesses, or even irritable bowel syndrome.

Our patients' prodromes were not just the typical rash of HAE, erythema marginatum; just as common were

tiredness, altered mental state and physical sensations. Prodromes were reported by 68%, which is slightly less than in 3 other studies that reported figures between 71% and 82.5% (24–26). The discrepancy may be explained by the retrospective nature of our study.

Forty-seven percent of our patients reported more than 12 attacks in the previous year. According to Cicardi et al. (27) one could consider long-term prophylaxis if the patient has more than 12 attacks a year. However, in a previous study, in which we used EQ5D-5L, we showed that HRQoL did not differ comparing a group with up to 15 attacks the previous year and a group with 16–30 attacks. Instead, in the group with more than 30 attacks the previous year, their HRQoL was reduced compared with the other groups (12). Because of the retrospective nature of our study, we did not assess the severity of the individual HAE attacks, which would have required a prospective design.

Factors that triggered attacks were mostly trauma, mental stress, infections, physical exertion and, in females, menstruation. Zotter et al. (28) have also reported similar triggers. Furthermore, in our study alcohol or low air temperature could trigger an attack in 4% and 3%, respectively.

During HAE attacks up to 43% of our patients experienced itching. However, the angioedema of HAE is often referred to as non-pruritic in the literature (1). Although itching is a subjective sensation, we expect patients to be able to differentiate itching from the tingling and/or painful sensation of skin swelling. Bradykinin is a well-established algogen, but its role in pruritus is less clear. In inflamed skin, such as in that of subjects with atopic dermatitis, bradykinin can induce pruritus (29). In experimental mice models, bradykinin has been shown to induce a scratching behaviour (30). If patients with HAE report red skin lesions together with itching, this might be misinterpreted as urticaria. Therefore, whealing of the skin should always be checked in order to differentiate HAE from histaminergic angioedema. Itching of the skin in patients with HAE needs further investigation.

We confirmed that females have more frequent HAE attacks and more total sick days per year, which is similar to other reports (11). We also showed that during pregnancy and treatment with oestrogen-containing contraceptives, females have more symptoms of HAE, which also is well known (9, 11). As for contraceptives, gestagens and intrauterine devices in general did not influence the disease course. These contraceptives are also recommended in females with HAE (11). Gestagens can also work as a prophylaxis against HAE attacks for some females (11). Only one patient had experienced an HAE attack during delivery. Thus women with HAE and their physicians should not be too worried about HAE attacks during vaginal delivery. Therefore, the recommendation is that during vaginal delivery there is

no need for prophylaxis, but acute treatment for HAE should always be available (11, 31).

The rate of caesarean sections in this population was 21%. In Sweden in 2013, the mean prevalence of caesarean section was 17%, so it seems that this procedure is not significantly more frequent in this population than among others (32).

PdC1INH was the best treatment for acute attacks. Icatibant was not yet available in Sweden at the time of the survey. Tranexamic acid had poor to no effect on all patients during an acute attack. We found that during laryngeal attacks, 26% of our patients had received glucocorticoids and 14% had received antihistamines, although these drugs are likely to be ineffective in HAE. These treatments may have been used because the diagnosis was unknown, or if the diagnosis was known, because the treating physician lacked appropriate knowledge. Because of high risk of recall bias we did not differentiate between treatments given before and after the diagnosis was established. As for maintenance treatment, attenuated androgens seem to be as effective as pdC1INH. At the time of study only 7 patients were having pdC1INH infusions regularly for maintenance treatment compared with 22 patients receiving attenuated androgens. In general, tranexamic acid did not reduce the number or severity of HAE attacks. In the World Allergy Organ guidelines, tranexamic acid is not recommended as a maintenance treatment, although it is also stated that it can have an effect on some patients (33). During recent years, i.e. after the completion of the present questionnaires, there has been a paradigm shift in the treatment of adults with HAE, as reported by Bygum (34). For example, more than half of the Danish patients with HAE stopped long-term prophylaxis with danazol or tranexamic acid and changed their treatment regimen to on-demand treatment with C1-inhibitor concentrate or icatibant (34). This fact highlights the need for a continuous prospective follow-up of patients with HAE, and documentation of data in national quality registries.

In both males and females, HAE caused frequent visits to healthcare institutions and also 5–10 days of sick leave yearly, which is a burden for the patient, the healthcare system and society. Wilson et al. (17) showed that, in the USA, the mean cost of a patient with HAE is approximately 42,000 US dollars per year. Other studies have also reported the burden of HAE imposed on society (12, 14–16).

The strength of our study is that we used a multidisciplinary approach, multimodal recruitments, and a telephone interview with a physician for clarification of responses in the written questionnaire, and for discussing patients' personal matters and reflections. A further strength is that we had the same interviewer through the whole study, thereby increasing consistency in questioning and interpretation. The prevalence found in

our present study indicates that we have made a census instead of a sample, although some subjects may not have been found. The limitation of this study is that it is retrospective, with a risk of recall bias. Furthermore, treatment regimens have changed during recent years and new therapies, such as icatibant, were not covered in the present study.

In conclusion, the prevalence of HAE was estimated to be 1.54/100,000 in Sweden, with type I being much more common than type II. Forty-seven percent of responding patients reported at least 12 attacks in the previous year. HAE affected females more severely than males, leading to twice as many days on sick leave in women. Attenuated androgens and pdC1INH reportedly had a good effect on preventing attacks, and pdC1INH in general had a very good effect on acute attacks. The shift in treatment regimen calls for a continuous follow-up in national or international quality registries.

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Conflicts of interest: PN has been a paid lecturer working for Shire, and has participated in advisory board meetings with CSL Behring. JB has participated in advisory boards for CSL Behring and Viropharma and worked as a consultant for CSL Behring, Shire and Viropharma. JB has also participated in clinical studies for Shire and Viropharma. LM is Global Medical Dermatology Lead for Pfizer, USA, but was working in a post-doctoral position in dermatology at the Karolinska University Hospital when the study was launched.

AL has been a paid lecturer working for Shire. C-FW has been a lecturer paid by Shire, Galderma and Novartis, and has participated in advisory board meetings with CSL Behring. MN has no conflicts of interests.

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