



CLINICAL RESEARCH STUDY

Hereditary Angioedema: New Findings Concerning Symptoms, Affected Organs, and Course

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ABSTRACT

PURPOSE: Hereditary angioedema (HAE) due to C1 inhibitor deficiency is clinically characterized by relapsing skin swellings, abdominal pain attacks, and life-threatening upper airway obstruction. Our aim was to examine a temporal and spatial pattern of the edema episodes by evaluating the long-term course of hereditary angioedema in order to establish a specific swelling pattern.

SUBJECTS AND METHODS: Data were generated from 221 patients with C1 inhibitor deficiency by asking them about symptoms they experienced during their edema episodes. Documentation was accomplished through the use of standardized questionnaires.

RESULTS: A total of 131 110 edema episodes were observed. Clinical symptoms started at a mean age of 11.2 (SD 7.7) years. During the following cumulative 5736 years, only 370 (6.5%) symptom-free years occurred. Skin swellings, including extremity, facial, genital, and trunk swellings, and abdominal attacks occurred in 97.4% of all edema episodes of the disease. The other episodes were laryngeal edema (0.9%); edema of the soft palate (0.6%); tongue swellings (0.3%); headache episodes (0.7%); episodes affecting urinary bladder (0.3%), chest (0.2%), muscles (0.4%), joints (0.1%), kidneys (0.1%), and esophagus (0.05%), and were partly combined with other edema episodes. The per-patient analysis and the per-episode analysis revealed markedly discrepant results. On average, women had a more severe course of the disease than men. Patients with early onset of clinical symptoms were affected more severely than those with late onset.

CONCLUSION: The described swelling pattern is specific for HAE and allows a tentative diagnosis based on clinical symptoms and the course of the disease. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Angioedema; Hereditary angioedema; C1 inhibitor deficiency

Hereditary angioedema (HAE) was first described clinically by Quincke¹ and Osler.² Classic HAE types I and II (Mendelian Inheritance in Man #106100) are associated with functional deficiency of C1-INH in plasma due to mutations of the C1 inhibitor gene.³⁻⁵ The defective C1-INH gene produces either no C1-INH (type I HAE) or a dysfunctional C1-INH (type II HAE). A third type of HAE was described a few years ago; this type is not associated with a C1-INH deficiency, and its related genetic defect is still not known.⁶

HAE due to C1-INH deficiency is clinically characterized by unpredictably occurring episodes of edema at var-

ious body sites followed by disease-free intervals of variable duration. Since the first descriptions of the disease, it has been well known that the skin, the gastrointestinal tract, and the upper airways may be affected; various reports have confirmed these results.⁷⁻¹² However, some basic features of the disease have not been investigated until now, namely, how frequently various organs and body sites are affected during the long-term course of the disease. Such an investigation examining frequency of HAE episodes at various skin regions and at frequently, as well as rarely, affected organs could reveal a pattern of edema that may be specific for HAE due to C1-INH deficiency. If such a pattern exists, valuable information for diagnosing HAE could be derived. The aims of the present article are to examine temporal

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patterns, spatial patterns, and associations among both types of patterns and additional parameters.

METHODS

Study Design

Our analysis was based on retrospective clinical case reports. We chose this design in order to obtain information not only about frequent complaints but also about swelling episodes at rare edema sites. Data were generated by asking patients about symptoms they experienced during episodes of HAE. Criteria evaluated were the frequency of episodes and their body sites at various ages of the patients. Documentation was accomplished through the use of standardized questionnaires and scores.

Patients

A total of 221 patients with C1-INH deficiency were surveyed in the angioedema outpatient service at the Department of Dermatology, University of Mainz, Germany. Diagnosis of HAE was made on the basis of patient history, clinical examination, and laboratory results, including deficiency of functional C1-INH and C4 in plasma. Patients came from 108 unrelated kindreds. Twelve of the 221 individuals with inherited C1-INH deficiency had no clinical signs of HAE. Seven of these 12 patients were children or adolescents below the age of 15 years; the others were 21, 37, 39, 41, and 61 years old. The 12 individuals belonged to 12 families in which other family members had symptomatic HAE.

The following data describe the 209 patients who presented with clinical symptoms of the disease. Types of HAE, age, sex, and laboratory results are summarized in Table 1. All patients had recurrent episodes of self-limiting edemas of the skin, intestinal tract, larynx, or other organs. Some patients experienced only a limited number of episodes, (ie, had 3 or fewer years with clinical symptoms [12 children, 2 adults]). This group of patients was excluded from the third part of the analysis (ie, examining disease severity and associations among different aspects of HAE) because they may not have had enough experience to report about the episodes. However, they were included in parts 1 and 2 of the analysis because we did not want to exclude patients at the beginning of the disease. In addition, in the third part we did not consider time periods when patients received long-term prophylaxis. Up to the end of 2004, the lifetimes of the here-described patients added up to 8443 years. The total number of years with clinical symptoms (between the first and last episode) was 5736. The sum of

symptom-free years, including the time before onset, was 2707 years.

Data Collection and Presentation

When the patients were seen for the first time, they were asked about the affected organs in all episodes they had experienced until that time. Then, for each individual organ, they were asked about the onset of the first episode and the frequency of edema episodes per year. The visit included a physical examination and laboratory confirmation of the diagnosis of HAE. Later, the patients were seen every 4 to 6 months during the first year and yearly thereafter. At each contact, frequency of episodes and affected body sites of the symptoms were assessed. In the follow-up examinations, the number of bouts of angioedema was determined by questioning the patients and by analyzing a swelling calendar that the patients filled out at home noting

time, duration, and severity of their angioedema episodes and the organs involved. Angioedema episodes were counted separately for abdominal attacks, laryngeal edema, uvular edema, tongue swellings, and episodes at the other rarely affected organs. Many skin swellings started at the hand and were limited to this region. Others started at the hand and extended during the following day or days to the

CLINICAL SIGNIFICANCE

- Hereditary angioedema due to a genetic deficiency of C1-esterase inhibitor shows a specific temporal and spatial pattern of edema episodes.
- The disease may not only affect the skin, gastrointestinal tract, and larynx, but also various other organs.
- On average, women have a more severe course of the disease than men.
- Patients with early onset of clinical symptoms are affected more severely than those with late onset.

Table 1 Clinical Symptoms and Laboratory Results Regarding 209 Patients From 108 Families with Hereditary Angioedema Due to C1-INH Deficiency

HAE Type I	
Patients	196
Families	102
Patients without affected family members	20
HAE Type II	
Patients	13
Families	6
Patients without affected family members	1
Age (years)	40.4 ± 17.8
Sex (M/F)	82/127
C1-INH protein (g/L)	0.049 ± 0.03
HAE Type I	
C1-INH protein (g/L)	0.29 ± 0.16
HAE Type II	
C1-INH activity (%)	16.9 ± 9.6
C4 (g/L)	0.09 ± 0.047

HAE = hereditary angioedema.

Normal range for C1-INH protein, 0.15 to 0.35 g/L.

Normal range for C1-INH activity, 70% to 130%.

Normal range for C4, 0.20 to 0.50 g/L.

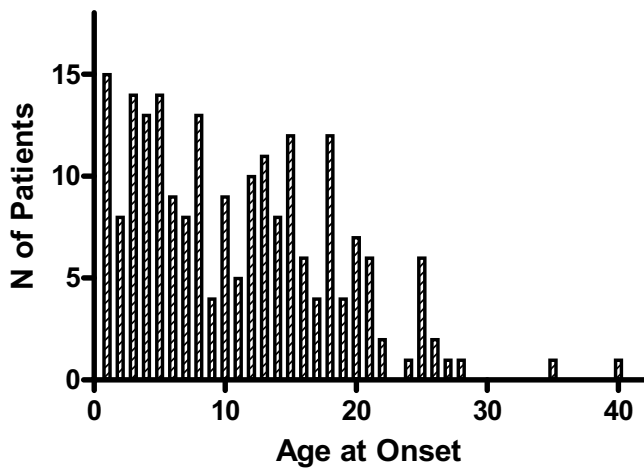


Figure 1 Age at onset of the clinical symptoms in 209 patients with hereditary angioedema due to C1 inhibitor deficiency.

whole arm; a similar pattern occurred for the lower extremities. Swellings at another extremity that followed directly after an initial extremity swelling (usually within a few hours or one day), as well as simultaneous swellings at one or more other extremities, were not counted as separate swellings. Data were presented on a per-patient and a per-episode basis. This procedure was followed because the per-episode basis is closer to the clinical view than the per-patient basis; however, the procedure does not provide independent data because some patients present with many episodes and others with only a few. No significance tests were performed on the per-episode basis.

Laboratory Methods

Protein levels of C1-INH antigen, C4, and C1q were assayed by radial immunodiffusion, and C1-INH activity was determined using the chromogenic substrate C₂H₅CO-Lys(ε-Cbo)-Gly-Arg-pNA (Immunochrom C1-INH, Technoclone, Vienna, Austria).

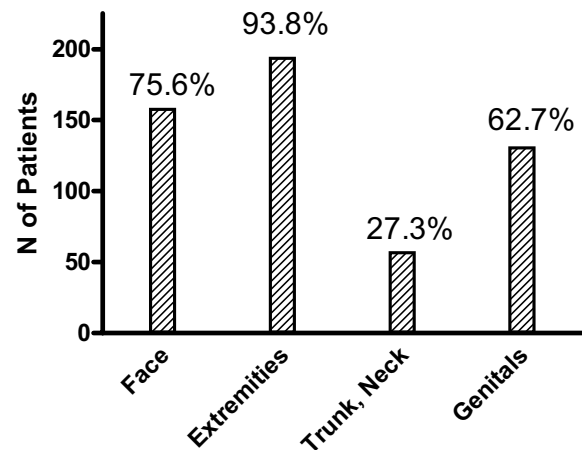
RESULTS

Temporal Pattern: Symptom-Free Periods and Years with Clinical Symptoms

Symptom-free periods lasting longer than 12 months include the years from birth to the first clinical sign of the disease and symptom-free years during the phase of clinical symptoms (due to either the natural course of the disease or prophylactic treatment). In most patients, clinical symptoms started in childhood or adolescence (Figure 1); the mean age at onset of the disease was 11.2 years (SD ±7.7, range 1 to 40 years). Onset of clinical symptoms occurred in the first decade of life in 107 patients, in the second decade in 79 patients, and later in 23 patients. In 15 of 209 patients, clinical symptoms started within the first year of life. From the onset of the first clinical symptoms until the time of data collection, the majority of patients (158 of 209) had recurrent swelling episodes without symptom-free intervals

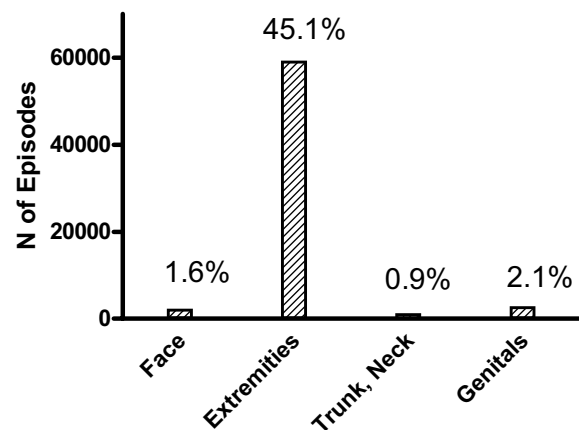
longer than 12 months. The remaining 51 patients had an average of 7.4 symptom-free years ranging from 1 to 34 years. Thirty-six of those 51 patients did not receive any prophylactic treatment during that time period, ie, their symptom-free years were part of the natural course of their disease. The other 15 of 51 patients were asymptomatic because the patients received long-term prophylactic treatment and responded very well to it; the average symptom-free duration was 10 years. Among the 209 patients, 34 were aged 60 years old or older (mean: 68 years, range 60 to 87 years). Thirty of these patients had experienced clinical symptoms as of the time of data collection (end of 2004). In the four other patients, the symptoms had ended 3, 7, 16, and 18 years previously.

A: per-Patient Analysis



N = 209 patients; column percents do not add up to 100% due to patients having multiple sites affected

B: per-Episode Analysis



percentage based on n = 131,110 episodes; column percents do not add up to 100% due to edema episodes in other organs

Figure 2 Location of skin swellings.

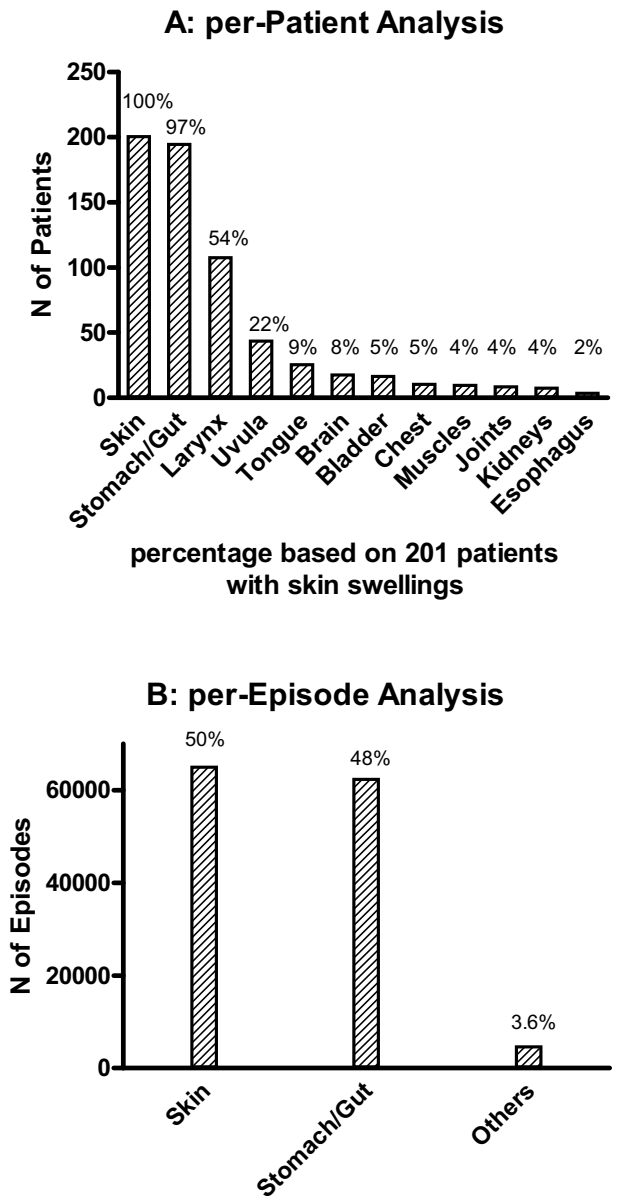


Figure 3 Frequency of skin swellings, abdominal pain episodes, and edema episodes in other organs.

Spatial Pattern: Swellings in Various Organs and Body Sites

During the symptomatic period a total of 131 110 edema episodes occurred. The distributions of skin swellings are shown in Figure 2 on a per-patient and a per-episode basis. The respective distributions of sites affected by the edema episodes are shown in Figure 3. The great majority of the edema episodes were skin swellings and abdominal attacks (Figure 3B). The frequency of episodes in the rarely affected organs (column 3 of Figure 3B) is shown in Figure 4.

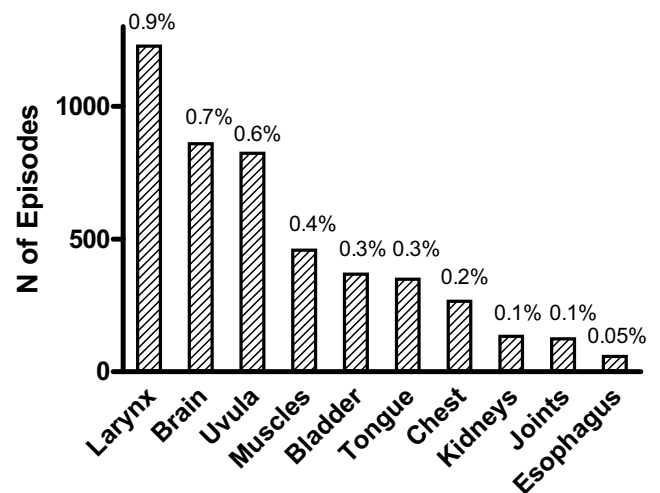
Skin Swellings

On a per-patient basis, recurrent skin swellings occurred in 201 of 209 patients; the 8 patients without skin swellings were children and adolescents aged 5 to 16. The total number of skin swellings observed was 65 102.

Swellings of the extremities. Of all 201 patients with skin swellings, 196 (97.5%) reported swelling of the extremities (hands and arms, feet, legs and thighs). Among the total number of 65 102 skin swellings, 59 095 (90.8%) affected the extremities; 34 884 (59.0%) of these swellings occurred at the upper extremities. Three patients reported blister formation in severe skin swellings. In 2 patients, blisters occurred in the crook of the elbow; in one patient, at the instep 1 day after onset of the skin swelling.

Facial swellings and their association with upper airway obstruction. On a per-patient basis, 158 of 201 (78.6%) of the patients with skin swellings had facial swellings, yielding a total of 2134 facial swellings. The per-episode view leads to a different result in this case: Only 2134 (3.3%), from the total of 65 102, skin swellings affected the face. Patients with facial swellings exclusively, ie, without any skin swellings at other body sites, were rare (5 patients, number of facial swellings: 14, 2, 1, 1, 1). In 50 of 158 patients (31.6%), 608 of 2134 episodes of facial edema (28.5%) extended to laryngeal edema at least 1 time.

Genital swellings and skin swellings in other regions. In the per-patient view, 131 of 201 (65.2%) of the patients with skin swellings had genital swellings lasting about 3 days. The per-episode view provides a result similar to that for facial swellings: among the total of 65 102 skin swellings, only 2741 (4.2%) affected the genitals. A figure of 57 of 201 patients (28.4%) had skin swellings of the trunk. Among the total of 65 102 skin swellings, 1132 (1.7%) affected the trunk.



percentage based on n = 131,110 episodes
Figure 4 Edema episodes at rare edema sites.

Abdominal Attacks

A large portion of patients—195 of 209 (93.3%)—had recurrent abdominal attacks. The 14 other patients consisted of 10 adults (22 to 65 years old) and 4 children (2 to 15 years old). All 14 patients had other family members with skin and abdominal involvement of the disease. The total number of abdominal attacks was 62 503.

Laryngeal Edema

Laryngeal edema was assumed when there were voice changes (deeper voice, hoarseness, aphonia) associated with dyspnea and fear of asphyxiation. Most patients also had a feeling of a lump, tightness of the throat, and dysphagia. Such episodes occurred in 108 of 209 patients (51.7%). The total number of laryngeal edemas was 1229—ie, only 0.9% of all 131 110 edema episodes. Isolated laryngeal edema, ie, laryngeal edema without a simultaneous edema of the soft palate or the tongue, occurred in 91 of 108 patients (84.3%) and 793 of 1229 episodes (64.5%). An edema of the uvula or the whole soft palate was associated with 207 of 1229 episodes of laryngeal edema in 28 patients. In 252 of 1229 episodes among 18 patients, there was a simultaneous tongue swelling.

Uvular Edema, Edema of the Soft Palate

A total of 44 of 209 patients (21.1%) had 826 of 131 110 episodes (0.6%) of edema of the uvula or the total soft palate including the uvula. In 28 patients with 207 of 826 episodes, there was an associated laryngeal edema. Sixteen patients had 586 edema episodes of the uvula/soft palate that occurred alone and were not associated with voice changes of a simultaneous laryngeal edema—ie, 586 of 826 (70.9%) occurred in isolation. In 1 patient the uvula was so enormously swollen that it was hanging outside of her mouth.

Tongue Swellings

Tongue swellings occurred in 26 of 209 patients. The total number of tongue swellings was 351. In 18 patients, 252 tongue swellings were associated with an obstruction of the upper airways (eg, dyspnea, voice changes). In 10 patients, 99 of 351 (28.2%) tongue swellings occurred in isolation, without laryngeal edema. Two patients had both kinds of tongue swellings (ie, with and without laryngeal edema) and, therefore, belong to both groups.

Headache Episodes

Eighteen patients (8 males and 10 females) reported about 862 episodes of severe headache. The headache episodes were not associated with edema episodes at other sites or organs. The severe headaches lasted for 4 hours to 4 days, in most patients for 1 to 2 days. The headache was accompanied by various other signs, including feeling of pressure in the head (18 patients), feeling of pressure in the eyes (18 patients), visual disturbances (6 patients) such as: blurred vision, double vision, difficulty in focusing, and narrowed visual field; also, giddiness (1 patient), disorders of balance (1 patient), ataxia (1 patient), impaired orientation (1 pa-

tient), vomiting (2 patients), and decrease in physical and mental powers (1 patient). No patient reported photophobia, sensitivity to noise, osmophobia, or an excessive urinary discharge following a headache episode. No female observed an association with menstruation. All patients reported that analgesics were not effective. Five patients received C1-INH concentrate because of 134 headache episodes (2 patients received 500 U because of 110 episodes, and 3 patients received 1000 U because of 24 episodes). The C1-INH concentrate was effective in all treated episodes. In most episodes relief occurred after 30 minutes, and in all treated episodes after 5 to 60 minutes.

Involvement of the Urinary Bladder and Urethra

Seventeen of the 209 patients reported an involvement of their bladder or their urethra. The 370 episodes lasted from 1 to 3 days and were not associated with abdominal attacks. In 6 patients and 136 episodes, skin swellings preceded the symptoms for 1 or 2 days or occurred simultaneously. All patients had strangury, urinary stammering, retention of urine in the bladder, or anuria. Pain at micturition was reported by 15 of 17 patients. Additional symptoms were painful spasms or stabbing pain of the bladder (7 patients). In one patient a cystoscopy revealed a marked edema of the mucosa of the bladder. One patient was a medical laboratory technician and made a urinalysis of the mid-stream urine in 19 of her 60 episodes; there were no pathologic findings. In 2 other patients urinalysis was also normal. Four patients received C1-INH concentrate for 60 episodes. Relief and resolution of the complaints occurred within 1 hour after the injection in all episodes.

Involvement of the Muscles

Ten patients reported a total of 461 episodes of muscle involvement lasting 2 to 3 days; all cases were characterized by a circumscribed induration of muscles. At the time of the palpable and painful muscle swellings, there were no skin swellings or attacks in other organs. The muscles of the dorsal region were affected the most (9 patients); the muscles at the back of the neck (2 patients), the shoulder (2 patients), the forearm (1 patient), and the pectoral muscles (1 patient) rarely were affected. Two patients received C1-INH concentrate for treatment of 3 episodes and reported a marked effect 1 hour after the injection.

Involvement of the Shoulder and Hip Joints

Four patients reported 55 unilateral pain episodes in the shoulder joint lasting 1 to 2 days. Fifty-one of the 55 episodes were associated with a skin swelling of the shoulder. One patient received 500 U C1-INH concentrate because of 2 pain episodes in the shoulder joint. Relief started after 1 hour, and the complaints disappeared 3 hours after the injections. Five patients reported 71 unilateral painful episodes of the hip joint lasting for 1 to 2 days. Pain increased when the patients were walking and, thus, led to limping. In 24 episodes, a skin

swelling of the thigh or buttock on the same side preceded or accompanied the joint complaints.

Chest Episodes with Breathing Difficulties and Feelings of Tightness and Pain

Eleven patients reported 268 retrosternal chest episodes with feelings of tightness and pressure in the chest and severe pain. Breathing was painful and, therefore, impaired and was associated with dyspnea. Breathing deeply was impossible because of stabbing pain. There was no associated edema at any other organ. One patient reported that he had the feeling that food could not pass through his esophagus at that time. There was no trigger for these episodes. The duration was 1 to 2 days. In 2 patients, during such episodes, radiographs of the chest and electrocardiograms were performed but revealed no pathologic findings. Electrocardiograms performed during the symptom-free intervals among all 11 patients were normal. No patients had signs of heart failure or coronary insufficiency. A total of 251 of 268 episodes occurred in patients between their 20th and 50th years of life. Two patients received 500 U C1-INH concentrate during 35 and 20 of these episodes, respectively; those patients reported relief 30 and 60 minutes after the injections, respectively. Four patients started long-term prophylaxis with danazol because of their frequent skin swellings and abdominal attacks; after the commencement of that regimen, 3 of the 4 had no further chest episodes with feelings of tightness, pain, and breathing difficulties, and 1 patient had mild and less frequent episodes.

Involvement of the Kidneys

Eight patients reported 136 episodes of renal pain. Three patients had renal colics, and the others had severe permanent pain. The episodes usually lasted 1 to 2 days, ranging 14 hours to 4 days. Four patients underwent diagnostic procedures: No renal calculi or inflammatory changes were found. Four patients received 500 or 1000 U C1-INH concentrate for 67 of these episodes; relief occurred after 20 to 30 minutes in 3 patients and in 1 patient after 1 to 2 hours.

Esophageal Involvement

Four patients had 60 episodes that they ascribed to an involvement of the esophagus. One patient had 50 such episodes. The episodes presented with pain in the region of the esophagus. During swallowing the pain moved through the whole esophagus along with the swallowed food. Pain was severe, "as if the esophagus was sore and too narrow" or "as if there were knives crosswise in the esophagus." Because of the pain, eating was impaired and for several hours was impossible. The episodes lasted 1 or 2 days. In 2 patients, 41 episodes were associated with abdominal attacks; in 4 patients, 19 episodes occurred without such attacks. One episode was associated with chest pain. Two patients received C1-INH concentrate for 5 episodes and reported that relief occurred 1 and 2 hours after the injection,

respectively; the episodes lasted a shorter time (8 and 10 hours, respectively, vs 24 hours).

CROSS MODAL PATTERN: DISEASE SEVERITY RELATED TO SEX, AGE AT ONSET, AND VARIATIONS AMONG DIFFERENT MEMBERS OF A FAMILY

Women Versus Men

To test for sex differences, we contrasted the group of patients having many episodes (>12 per year) with the group having fewer episodes. In the per-patient view, 46 of 117 women (39.3 %) and 44 of 78 men (56.4%) had 12 episodes or fewer per year. In 71 of 117 women (60.7%) and 34 of 78 men (43.6%), more than 12 episodes occurred per year. The difference is significant at $\chi^2_{(1)} = 5.50$, $P < .020$. The mean number of episodes per year was also higher in women (24.0) than in men (20.1).

Early Versus Late Onset of Clinical Symptoms

In about one third of the patients (64 of 209), clinical symptoms started at age 5 or earlier. These patients had a total of 50913 episodes during 1621 symptomatic years, or 31.4 ± 22.3 episodes per year on average. In another third (68 of 209 patients), clinical symptoms started at age 15 or later. These patients had a total of 24117 episodes during 1355 symptomatic years, or a mean of 17.8 ± 21.1 episodes per year. A *t* test revealed that the early-onset group had significantly more episodes per year than the late-onset group ($t_{130} = 3.60$, $P < .001$).

Variations of Severity of Clinical Symptoms in Affected Members of the Same Family

For this dimension, we evaluated the information concerning 55 families with 155 HAE patients. Subjects who had no second family member affected or had less than 1 year of symptoms were not regarded. Among all the patients, severity was classified according to 4 steps: mild (1 to 6 episodes per year), moderate (5 to 12 episodes per year), severe (more than 12 episodes per year), or very severe (more than 24 episodes per year). The maximal differences among different members of a family were determined; the differences varied between 0 and 3 steps. As shown in Table 2, in 12 of 55 families the severity of the 2 affected family members' symptoms was equal; within all other families, the severity of symptoms varied among the family members, sometimes considerably.

DISCUSSION

In this retrospective study, we analyzed a relatively large number of patients with HAE due to C1-INH deficiency and their edema episodes. For most HAE patients the time pattern resembled the following: after a symptom-free period, the onset of clinical symptoms occurred in childhood or adolescence. Only a small proportion of patients had

Table 2 Variability of Disease Severity of the Affected Members in 55 Families

Discrepancy of Disease Severity*	Number of Family Members Affected					
	2	3	4	5	6	> 6
None	12†	-	-	-	-	-
Max 1 step	11	5	-	1	-	-
Max 2 step	4	7	1	1	1	1‡
Max 3 step	4	5	1	-	-	1§

*For the definition of disease severity, see the text.

†7 families mild episodes only; 5 families severe episodes only.

‡8 members affected.

§10 members affected.

symptom-free periods due to the natural course of their disease, either with preceding and subsequent clinical symptoms or after the last clinical symptoms. Therefore, we can conclude that after onset of the clinical symptoms, the disease persists for a lifetime in the vast majority of patients.

Concerning the spatial pattern, our results demonstrate that most HAE patients suffer from recurrent skin swelling, recurrent abdominal pain episodes, and from rarely occurring laryngeal edema. This pattern of organ involvement, which reflects the 3 cardinal symptoms of HAE, is well known. In 1992 Agostoni and Cicardi observed skin involvement in 91% of 226 patients, abdominal pain episodes in 73%, and laryngeal edema in 48%.¹¹ These findings, however, provide insight only into the affected organs per patient, but no information about the frequency of single episodes in the different organs. Our results based on the per-episode view demonstrate that nearly all episodes consisted of skin swellings and abdominal attacks (96.5%). Laryngeal edema was rare (0.9%), although it showed a prevalence of 51.7% in the per-patient view.

Skin swellings are one of the cardinal symptoms of HAE. According to our results, we can presume that all adult patients with HAE have skin swellings; any exceptions would be very rare. Skin swellings at the extremities are a notable symptom; upper extremities are involved more often than lower. In some cases the edema may be so severe that blisters occur (tension blisters). Our data show that facial swelling is a relatively rare event. However, the associated risk of an upper airway obstruction is rather high. The skin swelling pattern specific for HAE due to C1-INH deficiency is the following: there usually are extremity swellings in which facial, genital, and, more rarely, trunk and neck swellings are intermingled from time to time. Very few patients do not fit this pattern, namely, patients in whom the first symptoms are facial swellings and who did not experience many skin swellings at all. This should not be regarded as a separate pattern because it is possible that it reflects patients at the beginning of their disease.

Abdominal attacks occurred in most of our patients; only 10 adult patients had skin swellings but never an abdominal attack. Symptoms different from skin swellings and abdom-

inal attacks are rare in HAE. Laryngeal edema is potentially life threatening, and many cases of asphyxiation have been reported.^{13,14} In our patient series, laryngeal edema occurred alone or was accompanied by swelling of the soft palate, including the uvula and the tongue. In a recent analysis of a smaller patient group (61 patients with 1 or more laryngeal edemas), we showed that the frequency of laryngeal edema compared with other swellings was 1:125.¹⁵ Our results demonstrate that edema of the uvula or the total soft palate is a distinct clinical symptom of HAE. It frequently occurs in isolation, ie, without an accompanying laryngeal edema and without a tongue edema. One patient with a recurrent isolated edema of the soft palate has been described, in whom this type of edema acted as a 1-way valve leading to severe dyspnea and fear of asphyxiation.¹⁶ Isolated tongue swelling is a very rare symptom of HAE. This result differs from ACE-I-induced angioedema, in which tongue swellings are considerably more frequent.^{17,18}

The 862 headache episodes reported by 18 patients seemed to be similar to migraine episodes. However, some clinical features typical for migraine were lacking in these episodes. The prompt response of patients to treatment with C1-INH concentrate in the 134 treated episodes provides a further argument that these headache episodes are symptoms of HAE. Isolated edema episodes of the urinary bladder and urethra seem to be a rare but clear symptom of HAE. This finding is supported by the clinical symptoms and patients' prompt response to C1-INH concentrate when treated. Up to now, one patient with an involvement of the bladder has been reported.¹⁹ Nielsen et al mentioned urinary infections during or after attacks.²⁰ Involvement of the muscles as well as shoulder and hip joints were not mentioned as symptoms of HAE until now. Although also rare, chest episodes are very significant for the affected patients. The relapsing occurrence of chest episodes in young patients and the patients' rapid responses to treatment with C1-INH concentrate identify these complaints as symptoms of HAE. The pathogenesis of the chest episodes is not clear. Renal and esophageal involvements have also not been mentioned until the present time.

Women seem to be affected more severely by HAE than men; we can only speculate about the reasons for that finding. Exposure to estrogen via oral contraceptives and hormone replacement therapy promotes the clinical symptoms of HAE.²¹ Periods of pregnancy and lactation are associated with an increased number of edema episodes, at least in some women. Menstruation and ovulation may trigger skin swelling and episodes of abdominal pain. Patients with an early onset of the clinical symptoms have a more severe course of the disease compared with patients with a late onset. As of now there is no adequate explanation for this phenomenon. The C1-INH deficiency itself obviously is not the reason, because there are a few patients with a C1-INH deficiency who have no clinical symptoms. The kind of mutation of the C1-INH gene, likewise, is not

responsible. According to our results, in most families there is a high variability in disease severity among the affected family members. Factors that contribute to swellings or protective factors that could explain the difference between patients with frequent episodes and patients with rare episodes have not yet been identified.

The present investigation has several limitations. It is partly a retrospective study; data regarding swelling frequency and swelling sites depend on patients' recall. We are aware that information about swellings that occurred a long time ago may not be precise; such imprecision is especially likely concerning information about swellings in frequent swelling sites, namely, swellings of the extremities and abdominal episodes. Information about rare swelling sites such as laryngeal edema or genital swelling is more precise, because the swellings usually are very significant for the patient and his or her relatives. A detailed comparison of retrospective and prospective data in HAE was performed by Bork et al and showed no major discrepancies.²² Despite these limitations, the study yields observations about a relatively large sample and spans a long time period.

CONCLUSIONS

The typical time pattern of HAE shows an onset of clinical symptoms in the first or second decade of life. The following years are characterized by recurrent attacks with only a minority of patients having symptom-free years in between. Through this study, a swelling pattern consisting of frequent and rare swelling sites and the corresponding episode frequencies has been established. This pattern is specific for HAE and allows a tentative diagnosis based on clinical symptoms. Our analysis also revealed that a number of organs including chest, muscles, joints, kidneys, and esophagus may be involved in HAE.

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