

# Clinical Studies of Sudden Upper Airway Obstruction in Patients With Hereditary Angioedema Due to C1 Esterase Inhibitor Deficiency

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**Background:** Hereditary angioedema due to C1 esterase inhibitor deficiency is clinically characterized by recurrent and self-limiting skin, intestinal, and laryngeal edema. Asphyxiation by laryngeal edema is the main cause of death among patients who die of hereditary angioedema. This study describes the age at which laryngeal edema first occurs, the time between onset and full development, and the effectiveness of therapy and prophylaxis.

**Methods:** Information on 123 patients with hereditary angioedema was obtained from medical histories and reports by the general practitioners, emergency physicians, and hospitals involved.

**Results:** Sixty-one patients (49.6%) experienced a total of 596 laryngeal edema episodes. The ratio of laryngeal edema episodes to skin swellings and abdominal pain attacks was approximately 1:70:54 in patients who had laryngeal edema. The mean (SD) age at the first laryngeal

edema was 26.2 (15.3) years. Nearly 80% of the laryngeal edemas occurred between the ages of 11 and 45 years. The mean interval between onset and maximum development of laryngeal edema was 8.3 hours. A total of 342 laryngeal edemas cleared spontaneously without treatment, and 208 laryngeal edemas were successfully treated with C1 esterase inhibitor concentrate. Despite long-term prophylactic treatment with danazol, 6 patients developed subsequent laryngeal edemas.

**Conclusions:** Laryngeal edema may occur at any age, although young adults are at greatest risk. In adults, the interval between onset of symptoms and acute risk of asphyxiation is usually long enough to allow for use of appropriate emergency procedures. To prevent a fatal outcome, it is essential to instruct patients and their relatives about the first signs of laryngeal edemas and the necessary procedures to follow.

*Arch Intern Med.* 2003;163:1229-1235

**H**EREDITARY angioedema (HAE) was first described clinically by Quincke<sup>1</sup> and Osler.<sup>2</sup> Currently, 3 types of HAE have been described. Classic HAE is a well-defined autosomal dominant disease (Mendelian Inheritance in Man online database No. 106100) caused by an inherited deficiency of functional C1 esterase inhibitor (C1-INH). Donaldson and Evans<sup>3</sup> discovered the underlying defect in 1963: the defective C1-INH gene produces either no C1-INH (type I HAE) or a dysfunctional C1-INH (type II HAE).

In type I HAE, which represents 85% of patients, plasma levels of C1-INH are 5% to 30% of normal values; in type II HAE, levels of C1-INH are normal or elevated. The 2 forms are clinically indistinguishable. More than 100 different C1-INH gene mutations have been described in HAE, including missense and nonsense mutations, large deletions, and frameshift and splice-site mutations.<sup>4,5</sup> The low C1-INH concentration permits activation

of the kallikrein-kinin system, the early steps of the classic complement pathway, and even the fibrinolytic system, with release of vasoactive peptides, among which bradykinin is considered to be most important. The exact prevalence of type I and II HAE is unknown; current estimates suggest that the disease affects between 1 in 10000 and 1 in 50000 persons.<sup>6</sup> Another type of HAE that is limited to females and not associated with C1-INH deficiency was recently described by our group (Mendelian Inheritance in Man No. 300268) and has been termed *type III HAE*.<sup>7</sup>

Classic HAE due to C1-INH deficiency is clinically characterized by relapsing, self-limited episodes of edema at various body sites—most often the subcutaneous tissue, wall of the intestine, and larynx. The recurrent edema attacks therefore appear as skin swellings, abdominal pain attacks with or without ascites, and episodes of upper airway obstruction. Other clinical features are rare and include episodes of tongue edema and swell-

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### Clinical Features and Laboratory Results of 123 Patients With HAE Due to C1-INH Deficiency

Variable	Patients Without Laryngeal Edema (n = 62)	Patients With Laryngeal Edema (n = 61)
HAE type		
I	60	57 (With 588 episodes of laryngeal edema)
II	2	4 (With 8 episodes of laryngeal edema)
Sex, M/F	24/38	26/35
C1-INH protein, mg/dL*		
Patients with HAE I	6.8 ± 2.1	7.6 ± 2.6
Patients with HAE II	34 and 41	37 ± 6.0
C1-INH activity, %†	9.9 ± 9.1	9.5 ± 7.2
C4, µg/mL‡	94 ± 46	102 ± 57

Abbreviations: C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema.

\*The normal range for C1-INH protein is 15 to 35 mg/dL.

†The normal range for C1-INH activity is 70% to 130%.

‡The normal range for C4 is 200 to 500 µg/mL.

ing of the soft palate. In patients with HAE, upper airway obstruction is usually a result of laryngeal edema; if patients with HAE die of their disease, laryngeal edema is the usual cause of death. The unforeseen and unexpected occurrence of laryngeal edema associated with the risk of asphyxiation is the most important feature of this disease. In patients with undiagnosed HAE, mortality has been reported in up to 30% to 50%.<sup>8,9</sup> Recently, 6 patients with HAE who had asphyxiation as a result of laryngeal edema were described.<sup>10</sup> Laryngeal edema in HAE always bears the risk of asphyxiation; however, it is a rare event in HAE. The aim of this study is to provide information on the frequency of episodes of laryngeal edema compared with edema episodes at other sites, the age at which episodes of laryngeal edema first occur compared with the age of onset of the other clinical symptoms, the age at which laryngeal edema occurs most frequently, the interval between onset and maximum development of the laryngeal edema (ie, the period when emergency measures can be performed), the triggers of laryngeal edema, and the efficacy of treatment and prophylaxis.

## METHODS

A total of 123 patients with HAE due to C1-INH deficiency were surveyed in the angioedema outpatient service at the Department of Dermatology, Johannes-Gutenberg University, Mainz, Germany, from 1973 to 2001. Diagnosis of HAE was made on the basis of patient history, clinical examination findings, and laboratory results, including deficiency of functional C1-INH and C4 in plasma. Protein levels of C1-INH antigen, C4, and C1q were assayed by radial immunodiffusion, and C1-INH activity was determined using the chromogenic substrate C<sub>2</sub>H<sub>3</sub>CO-Lys(ε-Cbo)-Gly-Arg-pNA (Technochrom C1-INH; Technoclone, Vienna, Austria).

All patients were provided with C1-INH concentrate (Berinert HS; Aventis Behring, Liederbach, Germany) for treatment in case of laryngeal edema. After the first presentation, the patients were seen every 4 to 6 months during the first year and every 12 months thereafter. In exceptional cases, the patients could only be contacted by telephone. The mean duration of follow-up was 7.1 years (range, 1-29 years); the me-

dian duration was 5.0 years. Data on HAE symptoms were collected from the patients' medical history, clinical examination, and follow-up records. In the subset of patients with laryngeal edema, additional information was obtained from the reports of hospitals and intensive care units where the patients had been treated for laryngeal edema. Further information was obtained from the patients' relatives.

## RESULTS

The 123 patients belonged to 67 unrelated kindreds. Type I HAE was present in 117 patients from 64 families, and type II HAE was present in 6 patients from 3 families. Of the patients with type I HAE, 20 had no other affected family members and presumably had new mutations. Clinical features and laboratory results of the patients with and without episodes of laryngeal edema are presented in the **Table**. The clinical signs of laryngeal edema were dysphagia; the sensation of a lump in the throat; a feeling of tightness in the throat; voice changes, including hoarseness and roughness; and dyspnea. In patients with progressed laryngeal edema, mostly fear of asphyxiation and aphonia also occurred. Some patients reported only minimal dysphagia and hoarseness; a full-blown laryngeal edema, however, could not be verified. Such events were difficult to classify and therefore not considered in this study.

Of the 123 surveyed patients, 62 had no laryngeal edema and 61 (49.6%; 35 females, 26 males) had experienced 1 or more episodes of laryngeal edema, for a total of 596. The number of episodes of laryngeal edema in the affected patients ranged from 1 to 200: 22 patients had only 1 episode; 22 patients, 2 to 5 episodes; 7 patients, 6 to 10 episodes; 4 patients, 11 to 20 episodes; 3 patients, 21 to 30 episodes; and 2 patients, 31 to 50 episodes of laryngeal edema. One patient had approximately 200 episodes of laryngeal edema, which was confirmed by his general practitioner and the hospital he attended. The 6 patients with more than 21 episodes of laryngeal edema could only estimate the total number of these episodes. Among the 19 patients 60 years or older, 15 had laryngeal edema.

## FREQUENCY OF LARYNGEAL EDEMA, SKIN SWELLINGS, AND ABDOMINAL PAIN ATTACKS

We compared the number of episodes of laryngeal edema with the number of skin swellings and abdominal pain attacks among patients with laryngeal edema. Because many patients had experienced a large number of skin swellings and abdominal attacks, the frequency of these symptoms could only be grossly estimated by the patients. In contrast, most patients remembered the exact number of their episodes of laryngeal edema since each attack usually was a dramatic event. We excluded the patient who reported approximately 200 episodes of laryngeal edema in all analyses considering the total number of laryngeal edema episodes, because such an extreme number of episodes of laryngeal edema has not been previously reported in the literature.

The total number of skin swellings among the remaining 60 patients with laryngeal edema was approxi-

mately 27700, and the number of intestinal edema episodes with abdominal pain attacks was approximately 21400. In contrast, only 396 episodes of laryngeal edema were reported by these patients. Therefore, the ratio of episodes of laryngeal edema to skin swellings and abdominal pain attacks was approximately 1:70:54 in patients who had 1 or more episodes of laryngeal edema. Hence, approximately 1 of every 125 episodes of edema affects the upper airways.

#### AGE AT ONSET OF LARYNGEAL EDEMA AND OTHER CLINICAL SYMPTOMS

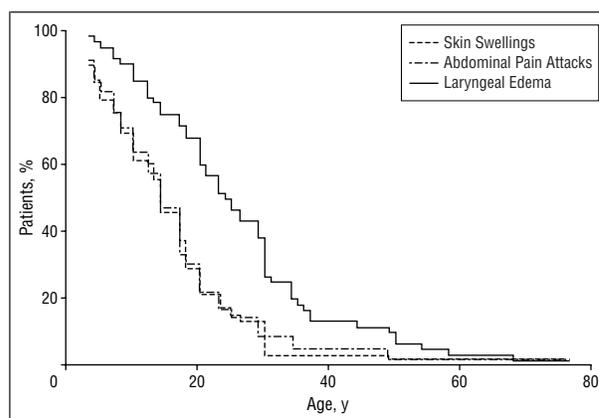
In the 61 HAE patients with laryngeal edema, the mean (SD) age at which they had their first laryngeal edema was 26.2 (15.3) years. In these patients, skin swellings began at a mean (SD) age of 15.4 (12.3) years, and abdominal pain attacks began at 16.2 (12.2) years. **Figure 1** shows the age at onset of the episodes of laryngeal edema, skin swellings, and abdominal pain attacks expressed as the symptom-free interval before the first of these edema episodes occurred. These findings confirm the earlier onset of skin swellings and abdominal pain attacks compared with laryngeal edema.

At the time of data recruitment, the patients were asked to report the time of the first and all subsequent episodes of laryngeal edema and the total number of episodes of laryngeal edema. The patient with 200 episodes of laryngeal edema was excluded from this analysis. **Figure 2A** shows that 312 (79.8%) of the 396 episodes of laryngeal edema occurred between the ages of 11 and 45 years. A total of 13 episodes of laryngeal edema (3.3%) occurred in children before 10 years of age, with the earliest occurring at 3 years of age. The oldest patient with sudden onset laryngeal edema was 78 years old.

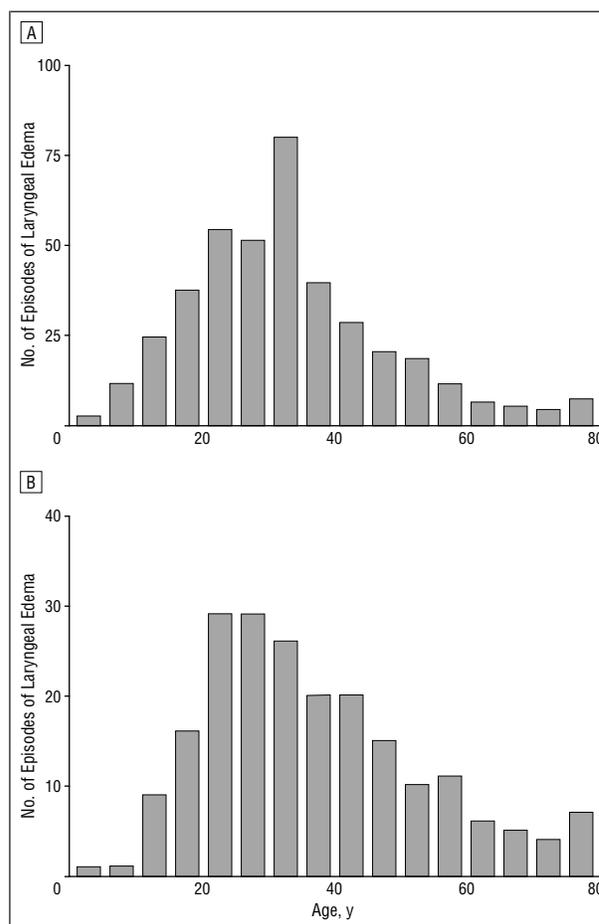
In our series, the 60 patients were of various ages at the time of data recruitment: 1 patient was younger than 19 years, 24 patients were between the ages of 20 and 39 years, 21 patients were between the ages of 40 and 59 years, and 15 patients were 60 years and older. Hence, the distribution as displayed in **Figure 2A** contains all of those 60 patients who had not yet reached older age and therefore could not have experienced episodes of laryngeal edema at an older age. Because a decrease in the occurrence of laryngeal edema is seen at the age of 40 years, we additionally analyzed the occurrence of laryngeal edema solely in those patients who were 60 years and older at the time of data recruitment. These patients had 209 episodes of laryngeal edema. As shown in **Figure 2B**, there was still a decrease in the occurrence of laryngeal edema at the age of 40 years. A total of 139 (66.5%) of the 209 episodes of laryngeal edema occurred between the 11th and 45th years of life. Hence, our conclusion that laryngeal edema occurs more frequently between the ages of 11 and 45 years, compared with younger or older patients, seems justified.

#### TIME BETWEEN ONSET AND MAXIMUM DEVELOPMENT OF LARYNGEAL EDEMA

Information about the interval between onset and maximum development of laryngeal edema was obtained from all 61 patients. As illustrated in **Figure 3**, 41 patients

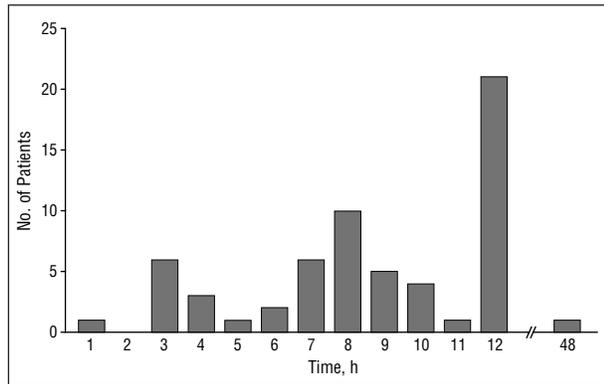


**Figure 1.** Age at onset of skin swellings, abdominal pain attacks, and episodes of laryngeal edema. Symptom-free intervals occurred in 61 patients with hereditary angioedema.



**Figure 2.** A, Age at which 396 episodes of laryngeal edema in 60 patients with hereditary angioedema occurred. B, Age at which 209 episodes of laryngeal edema in 15 patients 60 years or older with hereditary angioedema occurred.

(67.2%) reported that their episodes of laryngeal edema reached maximum development at 8 to 12 hours. Only 1 patient experienced a period shorter than 3 hours. This patient was a 9-year-old boy who had asphyxiation due to laryngeal edema that developed within 20 minutes, and that was the first clinical sign of his disease.<sup>10</sup> One adult patient reported a maximum development time of 48



**Figure 3.** Mean interval between onset and maximum development of episodes of laryngeal edema in 61 patients with hereditary angioedema.

hours for his 5 episodes of laryngeal edema. The mean time between onset and maximum development was 8.3 hours. Of the 39 patients with more than 1 laryngeal edema, 35 reported that the period between onset and maximum development of their episodes of laryngeal edema was essentially constant.

#### EDEMA SITES AND LOCAL TRAUMA PRECEDING EDEMA

In 83 (13.9%) of 596 episodes of laryngeal edema in 14 patients, a facial edema occurred before the laryngeal edema. In 1 patient, skin swelling of the neck preceded 1 laryngeal edema. Three episodes of laryngeal edema in 2 patients were associated with intestinal edema attacks.

Of the 596 episodes of laryngeal edema, 15 (2.5%) followed a direct and 10 (1.7%) followed an indirect local trauma: 10 episodes in 7 patients occurred secondary to dental surgery, and 5 episodes in 3 patients occurred within 24 hours after general anesthesia with intubation. In 2 patients, 10 episodes of laryngeal edema occurred after an indirect trauma (ie, subsequent to a trauma-induced lip swelling). The other 571 episodes of laryngeal edema in 49 patients all occurred spontaneously, that is, without any external trigger.

#### LARYNGEAL EDEMA COURSE IN PATIENTS WITH VS WITHOUT THERAPY

A total of 342 episodes of laryngeal edema cleared without drug therapy or emergency measures; these edema episodes all subsided spontaneously. Most of the patients were kept under the observation of an emergency physician. After a period of development lasting 8 to 12 hours in most patients, the symptoms persisted for 12 to 24 hours, after which they slowly subsided. The mean duration of symptoms was approximately 103 hours or 4.3 days.

A total of 254 episodes of laryngeal edema were treated with C1-INH concentrate, steroids, or emergency procedures.

#### C1-INH Concentrate

Twenty-five patients were treated for a total of 208 episodes of laryngeal edema with C1-INH concentrate. Patients received C1-INH concentrate from their general

practitioner or the emergency physician in case they experienced clinical signs of laryngeal edema regardless of the state of airway obstruction. Relief and resolution of symptoms occurred in 24 patients with 207 episodes within 30 to 60 minutes after the injection; in 1 patient, relief of symptoms did not occur until 4 hours later. The mean duration of laryngeal edema was considerably shorter among those who received C1-INH concentrate (15.0 hours) than among an untreated group of HAE patients (103 hours). All patients survived, and intubation or tracheostomy was not warranted for any of the episodes of laryngeal edema. Eighteen of these 25 patients with 193 episodes of laryngeal edema treated with C1-INH concentrate have been described previously.<sup>11</sup>

#### Steroids

Before the diagnosis of HAE was made, 16 patients had received steroid injections for 37 episodes of laryngeal edema. There was no therapeutic effect.

#### Intubation and Cricothyrotomy

Of 6 patients in whom laryngeal edema had progressed to a life-threatening state and threatened asphyxiation, 2 patients had to be intubated. Cricothyrotomy was necessary in 4 patients, 1 of whom required it for 3 episodes of laryngeal edema. All 6 patients survived. In an additional patient, attempts at intubation came too late and the patient died of asphyxiation.

#### Danazol

After the diagnosis of HAE was made, 32 of the 61 patients with 1 or more episodes of laryngeal edema per month (21 males, 11 females) received danazol as long-term prophylactic treatment (50 to 200 mg/d; mean duration, 7.4 years). After danazol treatment began, there was no further laryngeal edema in 26 of these patients. In contrast, 4 patients developed 1 laryngeal edema and 2 patients developed 2 episodes of laryngeal edema despite long-term prophylactic treatment with 100 mg/d of danazol. All 6 patients also developed skin swellings and abdominal pain attacks while taking danazol; however, these symptoms occurred less frequently than before initiation of prophylactic therapy.

#### FATAL OUTCOME BY ASPHYXIATION

Of the 123 patients, 120 are still alive. A 9-year-old boy with known C1-INH deficiency died of asphyxiation within 20 minutes of laryngeal edema onset. Intubation attempts by the emergency physician began 20 minutes after the first complaint but were not successful. The boy had had no clinical symptoms of HAE before the fatal event.<sup>10</sup> Two patients died at the ages of 72 and 77 years of other causes.

#### COMMENT

Hereditary angioedema due to C1-INH is a potentially life-threatening disease. Although the most frequent symp-

toms (relapsing attacks of skin swelling and abdominal pain) are not life-threatening, sudden airway obstruction may lead to asphyxiation.<sup>9,10</sup> Even the first episode of laryngeal edema may be fatal.<sup>10</sup> The fact that HAE may be associated with upper airway obstruction and death by asphyxiation has been known since descriptions of the disease by Quincke<sup>1</sup> and Osler.<sup>2</sup> Landerman<sup>8</sup> reviewed the literature in 1962 and stated that “almost all patients have recurrent episodes of abdominal pain and vomiting, and edema of the skin or pharyngeal-laryngeal area.” In a series of 226 HAE patients, 48% experienced episodes of laryngeal edema.<sup>12</sup> Other authors found rates of 28% (7 of 25 patients),<sup>13</sup> 50% (45 of 89 patients),<sup>14</sup> and 78% (81 of 104 patients).<sup>9</sup> One possible explanation for these various rates of patients having laryngeal edema might be that most of these studies did not consider that the patients differed in age. In our series, 15 of 19 patients 60 years or older (79%) had 1 or more episodes of laryngeal edema. We showed that laryngeal edema may occur at almost any age; the youngest patient in our series was 3 years old and the oldest was 78 years old. Our study reveals, however, that most episodes of laryngeal edema occur between the 11th and 45th years of life, indicating the age at which there is an increased risk of laryngeal edema. In a series of 29 HAE patients who died of asphyxiation due to laryngeal edema, 9 died between the ages of 21 and 30 years, indicating that it is particularly important to be aware of this possibility in this age group.<sup>10</sup>

To our knowledge, the relationship between single edema episodes and the involved organs had not been determined until now. The ratio of approximately 1:70:54 among laryngeal, skin, and intestinal edema episodes in this group of HAE patients with laryngeal edema confirms that laryngeal edema is a rare event; on average, only 1 of 125 edema attacks affects the upper airways in these patients. This, however, is only a gross estimate, since it is likely that patients remember having a bad attack of angioedema that caused laryngeal edema and forget having a mild attack of swelling of the foot or hand.

The mean age at which skin swellings and abdominal pain attacks occur for the first time is lower compared with that for laryngeal edema. In our series, the mean age at onset was 15 years for skin swellings, 16 years for abdominal pain attacks, and 26 years for laryngeal edema. It is extremely uncommon that the first clinical symptom of the disease might be a life-threatening laryngeal edema. However, this cannot be excluded, since we described a 9-year-old boy whose first clinical sign of C1-INH deficiency was a laryngeal edema with a fatal outcome.<sup>10</sup> We have not heard from any other patient whose first symptom was 1 or even several episodes of laryngeal edema without prior skin swellings or abdominal attacks.

The time between onset and maximum development of laryngeal edema is extremely important because that is the period available for emergency procedures, such as the administration of C1-INH concentrate, oxygen administration, intubation, or even cricotracheotomy. In a clinical analysis of 226 patients, the development time is mentioned as being “several hours.”<sup>12</sup> The results

reported herein show that the mean interval is 8.3 hours. None of the adult patients reported an interval of shorter than 3 hours. In 1 child, the time between onset and maximum development was only 20 minutes, and the child died of asphyxiation. In far-progressed laryngeal edema, dyspnea may progress to a life-threatening state more rapidly, even within several minutes. In 1 reported patient, an airway obstruction rapidly progressed during 5 minutes to the brink of respiratory arrest.<sup>15</sup>

Dental surgery and general anesthesia with intubation may trigger laryngeal edema. Intubation-induced laryngeal edema of HAE may present in a similar manner to postextubation laryngeal edema.<sup>16</sup> Local consumption of C1-INH by trauma-induced activation of the contact, coagulation, and fibrinolysis system may be responsible for the development of laryngeal edema secondary to dental surgery and intubation. Triggering by such external measures is rare. In contrast, more than 97% of laryngeal edema in the current study occurred spontaneously (ie, without any recognizable trigger).

In some patients, a facial edema may progress to laryngeal edema (eg, in 83 [13.9%] of the 596 episodes of laryngeal edema reported herein). However, far more facial edemas occur without evolving to a laryngeal edema. Thus, most episodes of laryngeal edema occur spontaneously and without preceding signs, so they are a continual threat to patients. The following factors lead to an increased risk of developing a laryngeal edema in HAE.

- Prior dental surgery or general anesthesia with intubation
- Age between 11 and 45 years
- History of 1 or more episodes of laryngeal edema
- Prior facial edema

Factors that lead to a decreased risk of developing a laryngeal edema include the following:

- Long-term treatment with attenuated androgens (eg, danazol or stanozolol)
- Age younger than 11 years or older than 45 years
- No prior laryngeal edema

Each laryngeal edema of HAE is potentially life-threatening. However, the course of the laryngeal edema is unpredictable. In our study, patients with approximately 30, 50, or even 200 episodes of laryngeal edema survived. On the other hand, we previously described 5 HAE patients who died of their first laryngeal edema and 1 female who had survived more than 100 episodes of laryngeal edema and then died of a subsequent laryngeal edema.<sup>10</sup>

Because of the danger of asphyxiation, it is vital that acute attacks of laryngeal edema be interrupted. Replacement therapy with purified C1-INH preparation has proved to be effective in treating relapsing skin swelling and acute attacks of abdominal pain in patients with HAE.<sup>9,17-20</sup> Information about treatment of laryngeal edema, however, with C1-INH concentrate is sparse.<sup>9,17-23</sup> In our series, 25 HAE patients received C1-INH concentrate because of 208 episodes of laryngeal edema. In 2000, we reported 193 episodes of laryngeal edema treated with

C1-INH concentrate in 18 of 25 HAE patients.<sup>11</sup> This approach was highly and rapidly effective. Relief and resolution of symptoms began 30 to 60 minutes after injection, and duration of the upper airway obstruction was substantially reduced.

Until now, C1-INH concentrate has not been available in many countries, including the United States. In Germany, all patients with HAE due to C1-INH deficiency are requested to store C1-INH concentrate in their refrigerator at home. In case of laryngeal edema, they receive 500 or 1000 U of C1-INH concentrate, regardless of the state of their airway obstruction. In choosing further treatment measures for laryngeal edema, consideration should be given to the degree of airway obstruction.<sup>14,15</sup> In mild cases of airway edema, careful observation of the patient in the hospital may be sufficient, and oxygen therapy may be provided. When the edema progresses and dyspnea occurs, ventilation via mask and further emergency procedures, including intubation and tracheostomy, may become necessary. If no other treatment is possible and asphyxiation is imminent, an emergency cricothyrotomy should be performed without delay.

Careful observation and appropriate and early management are extremely important in patients with airway compromise in HAE.<sup>14,15</sup> The possibility of sudden airway obstruction and asphyxiation must be emphasized in discussions with patients and their relatives, and attending physicians should be aware of this aspect of HAE. Patients' early recognition of the beginning of an episode of laryngeal edema is crucial. For this reason, patients should be carefully educated to recognize the first symptoms of upper airway obstruction.

In nearly all patients undergoing prophylactic long-term treatment with danazol or stanozolol, the numbers of skin swellings, abdominal pain attacks, and episodes of laryngeal edema are considerably decreased and the intensity of the episodes is milder. Therefore, these attenuated androgens are the most frequent choice for prophylaxis of edema in HAE due to C1-INH deficiency. However, adverse effects such as weight gain, headache, myalgia, anxiety, reduced libido, and arterial hypertension may limit their use. Adverse effects in females may additionally include menstrual irregularities and masculinization with occurrence of breast reduction, a deeper voice, and male pattern baldness. In the last years, the occurrence of hepatocellular adenoma and even liver cell carcinoma has been observed in patients with HAE receiving long-term treatment with danazol.<sup>24</sup> Because of these risks, it is necessary to establish the minimum dosage (50 to 200 mg/d of danazol) sufficient to suppress symptoms if treatment with danazol is needed. Currently, we have patients start with a prophylactic regimen of danazol in case they have severe attacks more often than once a month or have recurrent life-threatening laryngeal edema. However, a variety of limitations have to be considered, including the adverse effects described herein. Generally, we exclude young women and children from this kind of treatment.

Five patients with 6 subsequent episodes of laryngeal edema described herein show that despite pro-

phylactic treatment with 100 mg/d of danazol, additional attacks of laryngeal edema may still occur. We have not heard from other patients who received danazol and had episodes of laryngeal edema. There may be 2 reasons for the occurrence of laryngeal edema despite treatment with danazol. Generally, there is a small group of patients with HAE due to C1-INH deficiency who do not respond to attenuated androgens, and those 5 patients might have belonged to this group. The other reason could be that the daily dose of 100 mg of danazol might have been too low in these patients.

Some of the data in our study are based on the patients' anamnestic reports, which may limit the results. Despite these limitations, it can be concluded that laryngeal edema is a life-threatening condition in HAE that may occur at any age and that most commonly affects young adults. In adults, the interval between symptom onset and acute risk of asphyxiation is usually long enough to allow for appropriate emergency procedures, but this interval may be considerably shorter in children. Administration of C1-INH concentrate is promptly and rapidly effective. Laryngeal edema may occur despite long-term prophylactic treatment with danazol. Education of patients and their relatives about the first signs of laryngeal edema, which is usually unforeseen, and about the necessary procedures if a laryngeal edema occurs is essential to prevent a fatal outcome.

Accepted for publication August 14, 2002.

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#### Call for Photographs

##### *Archives of Internal Medicine Covers*

**W**ith the January 2003 issue, the *Archives of Internal Medicine* introduced photographs as cover art for the journal. Do you have a scenic photograph you have taken that you think would make a great cover shot? Submissions should be from our readers, reviewers, and authors, and must be formatted horizontally. They should be in color and at least 3.5 × 5 in but no larger than 8 × 10 in. Due to legal concerns, no recognizable people should appear in the picture. Please include your name and address and where the picture was taken. Send submissions to *Archives of Internal Medicine*, 1840 E River Rd, Suite 207, Tucson, AZ 85718. Cover photos will be chosen at the discretion of the ARCHIVES editorial staff. We look forward to seeing your photo on the cover of a future issue of the ARCHIVES!

*James E. Dalen, MD, MPH*  
Editor