

Review Article

Clinical management of hereditary angio-oedema in children

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Hereditary angio-oedema (HAE) results from the deficiency of C1-esterase inhibitor (C1-INH). The clinical picture of this autosomal dominant disorder is characterized by recurrent attacks of subcutaneous oedema and/or potentially life-threatening swelling of the submucosa. This review discusses the authors' decade-long experience obtained in the treatment and follow-up of pediatric patients with HAE. Twenty-six children with HAE were reviewed. Pedigree analysis was performed in all cases to identify afflicted relatives. C1-INH concentrate was reserved for the emergency treatment of acute oedematous attacks, whereas tranexamic acid and danazol were administered for short- or long-term prophylaxis. Follow-up care included laboratory tests and abdominal ultrasound, which was repeated at regular intervals. Twenty-one children had Type I HAE and five suffered from Type II HAE. Clinical manifestations of the disease first occurred in children when 2.5–12 years of age. Oedema formation primarily afflicted subcutaneous tissues. Mechanical trauma was identified as a precipitating factor in 20 patients. Pedigree analysis revealed 24 patients with relatives who suffered from HAE. Long-term prophylaxis with tranexamic acid or danazol was initiated in 11 patients; two children required short-term prophylaxis. No drug-related adverse effects were observed, except for one case of delayed menarche. Therapy improved serum complement parameters significantly and substantially reduced the frequency and severity of clinical episodes. Adequate prophylaxis and follow-up care can spare pediatric patients from oedematous attacks caused by HAE. Undesirable adverse effects can be avoided and the patient's quality of life enhanced considerably by administering the lowest effective drug dose.

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Hereditary angio-oedema (HAE) results from the deficiency of C1-esterase inhibitor (C1-INH) – a protein involved in the regulation of the classical pathway of complement activation (1,2). Although the exact prevalence of HAE in the European population is not known, indirect estimates indicate that it may be as high as 1 in 10,000–50,000 (3). The gene of the C1 inhibitor protein is located in the 1,2-q13 subregion of human chromosome 11. The disorder caused by the mutation of this gene is inherited as an autosomal dominant trait, producing two phenotypes of HAE (4). Type I HAE is characterized by

low antigenic activity and low serum levels of C1-INH. In Type II HAE, however, serum levels are normal or elevated but the C1-INH protein is non-functional (5).

C1-INH regulates the activity of four closely inter-related cascades, that is, the coagulation, fibrinolytic, kinin, and complement systems. The lack of C1-INH or its activity leads to abnormal activation of the classical complement pathway, which in turn reduces C4 and C2 plasma levels. C2 fragments produced during complement activation generate vasoactive, kinin-like mediators (C2-kinins). Additionally, tissue damage

induces the transformation of prekallikrein into kallikrein by the Hageman-factor, and bradykinin is released from high-molecular-weight kininogen. These mediators enhance capillary permeability and are presumed to be jointly responsible for precipitating recurrent oedematous attacks (6).

Angio-oedema can develop in subcutaneous tissues (of extremities, genitals, the face, or trunk) or involve the mucous membranes of the upper airways and the gastrointestinal tract. Submucosal oedema of the larynx or pharynx can cause suffocation, whereas the oedematous swelling of the intestinal wall may mimic the clinical manifestations of an acute abdominal catastrophe (3,7,8).

According to current therapeutic guidelines, the treatment of HAE comprises the following stages:

- (1) The treatment of acute oedematous attacks.
- (2) Short-term prophylaxis.
- (3) Long-term prophylaxis.

In the emergency treatment of acute attacks, C1-INH concentrate is currently preferred to fresh-frozen plasma (the erstwhile treatment of choice) (9–11). Prophylactic treatment is implemented through the administration of attenuated androgens (12,13), anti-fibrinolytic agents (14), or – in selected cases – C1-INH concentrate (15).

Although excellent reviews on HAE (3,7) have been published, searching the literature yields only a few publications on the treatment and follow-up care of pediatric patients. This paucity of relevant information prompted us to review our extensive experience (of longer than 10 years) in the therapy of children suffering from HAE.

Patients and methods

Patients

Between 1987 and 2000, 90 patients were registered in the database of the Hungarian HAE Center. The clinical data of 26 pediatric patients from 19 families are reviewed below.

The male-to-female ratio was 11 : 15, and age at the time of diagnosis ranged from 2.5 to 15 years (mean: 7.3 years).

Laboratory methods

CH₅₀ total complement levels were measured by the standard haemolytic titration method, using sensitized sheep erythrocytes (16).

The C4 complement fraction was determined by single radial immunodiffusion using anti-C4 antibodies (ATAB; Stillwater, MN, USA) and results were expressed as the percentage of

standard, normal serum values (17). The C1-INH level was also measured by radial immunodiffusion.

C1-INH activity was measured by kinetic assay, using a commercially available diagnostic kit (Behringwerke AG, Marburg, Germany). The activity of the C1 inhibitor in serum was determined by photometry and expressed as the percentage of standard, normal values.

Follow-up protocol

The first occurrence, frequency and localization of clinical manifestations, the duration of the disease, and potential precipitating factors of oedematous attacks, were ascertained. In addition:

(1) A pedigree analysis was performed in all patients.

(2) Long-term prophylaxis was elected if oedematous attacks recurred frequently (≥ 1 attack per month) or a life-threatening episode could be identified in the history.

(3) The following tests were performed in patients receiving long-term danazol prophylaxis:

- anthropometric assessment of growth (comparison of body height and weight development to age-specific normal values);
- bone age determination (hand X-rays);
- development of secondary sexual characteristics and time of puberty compared to a control population; and
- mental development (performance at school).

(4) Short-term prophylaxis was administered before surgical or diagnostic procedures were performed on the head and neck.

(5) Changes in the levels of serum complement fractions and clinical manifestations were monitored during therapy. Potentially drug-related adverse effects of treatment were also recorded.

(6) In patients undergoing long-term prophylaxis, laboratory tests (complete blood count, liver function tests, creatine kinase [CK] activity, and urinalysis) were repeated at 3–4-month intervals, whereas abdominal ultrasound was performed semi-annually during the first 2 years of treatment. Subsequently, asymptomatic individuals or patients with mild symptoms were checked every 6 months in order to detect potential liver damage.

(7) Patients with an acute attack of sub-mucosal (laryngeal or severe abdominal) oedema were always hospitalized and an abdominal ultrasound was performed if the attack involved the gastrointestinal tract. Hospitalization for an acute abdominal attack was considered justified when the following criteria were fulfilled:

- the presence of other acute abdominal pathologies could not be ruled out with certainty;
- manifestations were severe, that is, the attack was associated with obvious signs of hypovolemia (paleness of skin, prostration, dehydration, tachyarrhythmia) and included recurrent paroxysms of acute colicky pain unresponsive to symptomatic therapy; nausea and vomiting, or profuse diarrhea.

(8) The C1-INH concentrate used in this study was screened for hepatitis B and C by the manufacturer. Nevertheless, in observance of the safety precautions pertinent to blood products, hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) specific antibody were tested using commercially available immunoassays in all patients who had received the C1-INH concentrate.

Drug therapy

Acute oedematous attacks were treated by administering C1-INH concentrate (Berinert P injection; Centeon, Pharma GmbH, Vienna, Austria), whereas epsilon-aminocaproic acid (ϵ -aminocaproic acid) (Acepramin; Pannon Pharma, Budapest, Hungary), tranexamic acid (Exacyl; Sanofi Synthe Labo-Chinoin, Budapest, Hungary), and danazol (Danoval; KRKA, D.D., Novo Mesto, Slovenia) were used for prophylaxis.

Results

The initial manifestations of HAE were observed in children within the age-range of 2.5–12 years (median 5.9 years). Six children were asymptomatic at the time of diagnosis, which was established only after HAE had been ascertained in their symptomatic parents. Pedigree analysis revealed familial occurrence of the disease in 24 patients (from 19 families), but failed to identify HAE in the first-degree relatives of two children. Therefore, in these patients the C1-INH deficiency must have resulted from a new gene mutation (Table 1). The localization of clinical signs was variable. In the majority of patients (20 children; 76%), oedema formation involved subcutaneous tissues, whereas gastrointestinal manifestations occurred in 14 patients (53%) and laryngeal oedema developed in seven (26%). Subcutaneous oedema of the extremities and genitals usually persisted for 2–3 days, then resolved spontaneously. Oedematous swelling of the skin was not accompanied with itching, but caused an unpleasant sensation of distension

within the involved region. In eight children, a generalized, non-pruritic skin rash (erythema marginatum) was observed before and during oedematous attacks of HAE. The exploration of potential precipitating causes invariably identified mechanical trauma; however, upper airway infection was another important factor (Table 2). According to the results of serum complement studies, 21 children had Type I HAE, whereas five suffered from Type II HAE (Table 3).

All children with an acute oedematous attack (laryngeal oedema or severe acute abdominal complaints) were hospitalized. Emergency treatment was implemented by the parenteral administration of 500 U of C1-INH concentrate exclusively (Table 4). The injection accomplished substantial symptomatic relief within 30–60 min. This was accompanied with the regression of oedematous swelling; however, complete resolution of clinical signs and symptoms took 24–48 h. Administration of an additional 500-U dose (i.e. a 1000-U cumulative dose) was necessary in two patients (one with laryngeal and diffuse facial oedema and one with acute abdominal attack) to achieve a satisfactory rate of improvement. All patients hospitalized with an acute abdominal attack underwent abdominal ultrasound examination. Ascites was invariably ascertained in all cases whereas oedema of the intestinal wall was detected in 80% of patients (Fig. 1). As evidenced by follow-up ultrasound, appropriate treatment (C1-INH concentrate) achieved complete disappearance of free peritoneal fluid and oedematous swelling of the intestinal wall within 48 h.

Long-term drug prophylaxis with anti-fibrinolytic agents (tranexamic acid or ϵ -aminocaproic acid) was initiated in 11 patients owing to a frequent (weekly or monthly) recurrence of

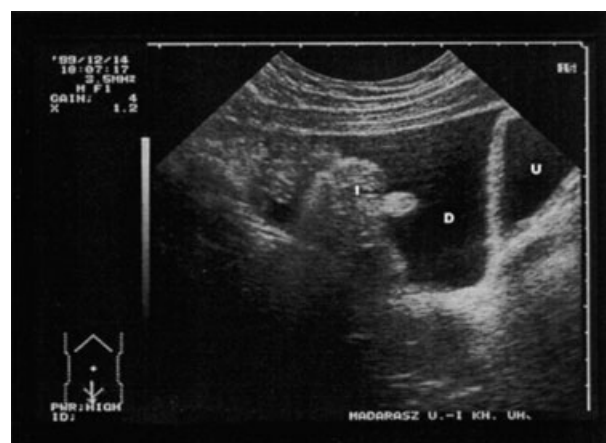


Fig. 1. Ultrasound during an acute abdominal attack. I, intestinal wall; D, free peritoneal fluid in the cul-de-sac; U, urinary bladder.

Table 1. Demographic properties of the 26 pediatric patients

Number	Initials	Gender	Age at diagnosis (years)	Age at onset of clinical manifestations (years)	Length of follow-up (years)	Pedigree analysis
1	Sz.Sz.	Female	10	9	1	F
2	V.Zs.	Female	10	5	2	→
3	V.P.	Male	5	→	1	M
4	S.T.	Male	7	7	11	M, sibling
5	S.P.	Male	13	12	11	M, sibling
6	S.L.	Male	11	11	1	M, sibling
7	M.J.	Male	5	4	6	M
8	K.Sz.P.	Male	7	5	5	F
9	K.F.	Male	8	5	6	F
10	K.T.	Male	7	7	6	F
11	G.Gy.	Male	11	3	2	→
12	S.T.	Female	7	3	1	M, sibling
13	P.D.	Female	3	→	1	F
14	O.A.	Female	5	2.5	1	M
15	M.R.	Female	3	6	9	M, sibling
16	M.I.	Female	7	5	9	M, sibling
17	N.I.	Female	6	6	7	M
18	H.K.	Female	14	9	6	F
19	B.L.T.	Female	3	3	19	M
20	K.Sz.H.	Female	15	→	1	F
21	Ö.B.	Female	8	6	11	F
22	M.Zs.	Male	8	4	2	F
23	K.Zs.	Male	12	→	1	F, sibling
24	K.É.	Female	11	→	1	M, sibling
25	K.K.	Female	1	6	1	M, sibling
26	K.Kl.	Female	9	→	1	M, sibling

F, father; M, mother; →, no affected family member.

Table 2. Clinical characteristics of the 26 pediatric patients

No.	Site involved			Precipitating factors			
	Subcutaneous	Laryngeal	Abdominal	Trauma	Stress	Infection	Menstruation
1	+	–	+	+	–	+	–
2	+	–	+	+	–	–	–
3	None						
4	+	+	+	+	–	+	–
5	+	–	–	+	–	+	–
6	+	–	–	+	–	–	–
7	+	+	+	+	–	+	–
8	+	+	+	+	+	+	–
9	+	–	–	+	–	–	–
10	+	–	–	+	–	–	–
11	+	–	+	+	–	+	–
12	+	+	+	+	–	+	–
13	None						
14	+	–	–	+	–	–	–
15	+	–	+	–	–	–	–
16	+	–	+	+	+	+	+
17	+	–	+	+	+	–	–
18	+	–	+	+	+	+	+
19	+	+	+	+	+	+	+
20	None						
21	+	+	+	+	+	+	+
22	+	+	–	+	+	+	–
23	None						
24	None						
25	+	–	+	+	–	+	–
26	None						

Table 3. Complement values at the time of diagnosis

No.	CH ₅₀ (48–103 CH ₅₀ /ml)	C4 (36–144%)	C1-INH level (64–166%)	C1-INH activity (>70%)	Type of HAE
1	15.1	30	19	1.4	I
2	31	15	233	22.5	II
3	31	24	43	47.5	I
4	41	9.2	214	0	II
5	23	21	297	0	II
6	5	5	5	1.5	I
7	41	5	24.1	0	I
8	17.1	2	19.4	14.5	I
9	48.6	23	17	36.1	I
10	28.8	17.2	30.8	17.5	I
11	27	6.4	23	9.7	I
12	5	38	5.8	7.2	I
13	50	20.8	36.4	10.2	I
14	51	6.5	21	13	I
15	41	17	250	14.3	II
16	22	15	311	6.8	II
17	58.8	12.4	21.1	12	I
18	39.6	6.2	15.1	15.5	I
19	24	15	18	0	I
20	26	18	48	23.5	I
21	38.4	15	12.6	35.5	I
22	5	12	15	21	I
23	29	8.1	19	21.2	I
24	47	25	30	59.8	I
25	87	14	36	63.7	I
26	69	5	23	49.1	I

C1-INH, C1-esterase inhibitor; CH₅₀, 50% complement haemolytic unit; HAE, hereditary angio-oedema.

Table 4. Frequency of symptoms and type of treatment in the 21 pediatric patients

No.	Symptoms*			Therapy†			
	N	R	F	Tranexamic acid	Danazol	Duration of treatment	C1-INH concentrate cumulative dose/attack
1			•	2 g/day		Long-term (1 year)	2×500 U
2		•		2 g/day		For symptoms only	
3	•						
4			•		200 mg/day	Long-term (11 years)	3×500 U
5			•		100 mg/day	Long-term (11 years)	
6		•					
7			•		100 mg/2 days	Long-term (6 years)	3×500 U+1×1000 U
8			•		100 mg/3 days	Long-term (4 years)	4×500 U
9		•					
10		•					
11			•		100 mg/2 days	Long-term (2 years)	2×500 U
12			•	1 g/day		Long-term (1 year)	3×500 U
13	•						
14		•					
15		•					
16		•		2 g/day		For symptoms only	
17		•		2 g/day		For symptoms only	
18			•		100 mg/2 days	Long-term (5 years)	3×500 U
19			•		200 mg/day	Long-term (11 years)	2×500 U+1×1000 U
20	•						
21			•	2 g/day		Long-term (1 year)	1×500 U
22			•		100 mg/day	Long-term (8 years)	
23	•						
24	•						
25		•		2 g/day		For symptoms only	
26	•						

*N, none; R, rare (< one attack per month); F, frequent (≥ one attack per month).

†Epsilon (ε)-aminocaproic acid is not shown as it had no effect or caused intolerance and therefore it was replaced with tranexamic acid.

C1-INH, C1-esterase inhibitor.

oedematous attacks, or because of the presence of life-threatening attacks in the case history. Complete remission was achieved in three girls maintained on 1–2 g/day of tranexamic acid; however, anti-fibrinolytic agents were ineffective in eight patients. Transferring these patients to treatment with 100–200 mg/day of danazol completely eliminated serious oedematous attacks (Table 4). In order to taper the cumulative dose, the dosage interval of danazol (100 mg) was increased to 2–3 days after 6 months of clinical remission. Switching to this intermittent regimen (i.e. doses repeated every other day or at 3-day intervals) from continuous dosage was successful in four patients. In patients maintained on long-term prophylaxis, doubling the daily dose for several days aborted prodromal symptoms or prevented the progression of mild clinical manifestations to full-blown attacks. A similar protective effect was observed in patients exposed to a precipitating factor (e.g. upper airway infection or mechanical trauma).

No adverse effects were potentially related to long-term prophylaxis and that would have necessitated the withdrawal of treatment if it were observed. The bone age, skeletal growth, and weight development were not substantially different from the age-specific averages of the Hungarian pediatric population. The time of the appearance of secondary sexual characteristics and the onset of puberty were also similar in seven children – menarche was delayed (to the age of 19 years) and menstruation was irregular in one girl. Hirsutism was not observed in patients receiving long-term danazol prophylaxis. Monitoring of laboratory parameters revealed normal values in all 11 children tested and abdominal ultrasound did not show any abnormality. The efficacy of danazol treatment was demonstrated by the significant increases of C4 and C1-INH concentrations in the serum (Fig. 2).

Nine children had mild, subcutaneous symptoms only and even these resolved spontaneously within 2–3 days. Accordingly, long-term prophylaxis was withheld and treatment was administered only when prodromal symptoms and signs occurred. In four patients, tranexamic acid (2 g/d) given for 2–3 days reduced the severity and duration of subcutaneous manifestations. Follow-up visits were scheduled at 6-month intervals for these children.

Short-term prophylaxis was necessary in two boys (11 and 14 years of age) undergoing dental extraction, because both had facial and laryngeal oedema precipitated by similar procedures in their history. Danazol (300 mg/day) initiated

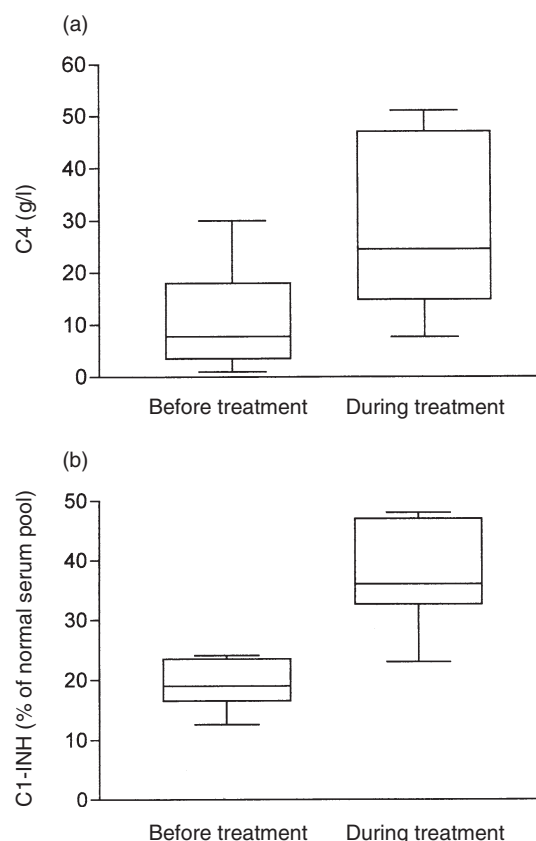


Fig. 2. Effect of long-term treatment with danazol on serum C4 (a) and C1-esterase inhibitor (C1-INH) (b) levels of children with hereditary angio-oedema (HAE) (box-and-whisker plots). Baseline values are compared to those measured in the first serum sample obtained after initiation of treatment. C4 levels were determined in eight children. Patients with high concentrations of non-functional C1-INH (233, 214, and 297%) were excluded from the comparison. Danazol treatment significantly increased both C4 and C1-INH levels ($p = 0.002$ and $p = 0.0156$, respectively, Wilcoxon's signed rank test).

4 days before and continued 4 days after dental treatment successfully prevented oedema formation.

The elimination of known precipitating factors also substantially reduced the incidence of oedematous attacks.

Discussion

HAE is an uncommon but life-threatening disorder. In unrecognized cases, the mortality of acute oedematous attacks is still ≈ 25 –30% and, consequently, early diagnosis is essential (7). In 80% of cases, diagnosis is facilitated by a known family trait of the disease. In the remaining 20% of cases – where no afflicted relatives can be identified – HAE results from a new gene mutation (18). In our pediatric population, the proportion of such cases was 93% and 7%, respectively. According to the

literature, 85% of HAE patients suffer from Type I, whereas 15% have Type II disease (7). The percentage distribution of Type I and Type II cases was 81% and 19%, respectively, in our series.

In general, the clinical manifestations of HAE first develop in children before they reach 6 years of age (3) – the median age of our study population was 5.9 years. However, no occurrences have been observed in newborns, and only one infant (19 months old) case has been reported (11). According to our experience, adolescence is often associated with substantial changes in the activity of the disease – particularly in girls – and this warrants closer follow-up during this period. In particular, clustering of oedematous attacks during the menstrual period was observed in 4 girls. Nowadays, contraception is initiated in early adolescence. However, oral contraceptives can precipitate acute attacks and are therefore not recommended for girls with HAE (3).

The incidence and severity of characteristic manifestations shows substantial inter-individual variation. Less than 5% of HAE patients are asymptomatic and 25% have symptoms only sporadically. Manifestations of the disease are common in 70% of patients and severe in 30% of this subpopulation (3). Eleven out of the 26 children followed up in this study had frequent and severe attacks. Usually, mechanical trauma is the most common precipitating factor. This is confirmed also by our experience, but upper airway infection was another potential triggering factor. Considering the importance of physical activity and sports on growth and development, restrictions on these should be determined carefully and individually. In children – as in adults – oedema of the extremities is the dominant manifestation, and abdominal attacks are more common than laryngeal oedema (3,7). Nevertheless, even rare occurrences of laryngeal oedema should be considered real emergencies. Owing to the small diameter of upper airways in children, relatively mild swelling of the mucosal lining causes substantial obstruction and therefore suffocation can ensue rapidly. In view of these risks, referral to intensive care is justified to monitor the clinical course and to ascertain the efficacy of treatment – repeated administration of C1-INH concentrate may be necessary to achieve satisfactory control of oedematous manifestations. This fact, and the ineffectiveness of conventional agents (e.g. antihistamines, corticosteroids, and epinephrine) account for the invariably high mortality of the disease and emphasize the importance of accurate diagnosis.

The striking similarity between the clinical manifestations of abdominal HAE attacks and surgical emergencies is an apparent diagnostic pitfall. Failure to evade this trap often leads to unnecessary interventions on patients already prostrated by the consequences of the acute oedematous attack (8,19). Reviewing the medical history of our patients up to the time of diagnosis revealed that two children had undergone exploration or laparoscopy during an acute abdominal attack – one of them twice! These interventions, however, were unwarranted as no abnormality other than the oedematous swelling of intestinal wall was ascertained. In order to elude this diagnostic pitfall, close monitoring of the patient, volume replacement, parenteral medication, and assessment of therapeutic efficacy, are necessary; all of this can be achieved by observing the patient for 24–48 h. Abdominal ultrasound is a non-invasive and readily accessible diagnostic test that yields reproducible results – particularly advantageous in pediatric practice (20). Therefore, free peritoneal fluid and oedema of the intestinal wall are invaluable sonographic clues for distinguishing abdominal HAE attacks from other pathologies commonly associated with ascites formation (intra-abdominal inflammation, autoimmune disease, tumors, etc.). When all other acute abdominal disorders have been ruled out, C1-INH concentrate should be administered to afebrile patients without laboratory abnormalities – and particularly to those with known HAE. Evidently, the occurrence or lack of prompt symptomatic relief after the administration of C1-INH concentrate confirms or refutes the tentative diagnosis.

In life-threatening HAE attacks, appropriate measures include the administration of fresh-frozen plasma. This preparation contains C1-INH; however, its use may be associated with alloimmunization or the transmission of infections (3,16). The most appropriate therapy is the intravenous administration of C1-INH concentrate. Its dosage is the same for both children and adults (i.e. 500–1000 U) (11). In this study, acute HAE attacks were treated with C1-INH concentrate exclusively. This approach was highly effective – clinical symptoms resolved within 1 h – and was not associated with adverse effects. C1-INH concentrate has been suggested as an ideal agent for permanent substitution, particularly for pediatric patients. Unfortunately, the short (72-h) half-life and high cost (\$310 per vial) of the concentrate preclude its use for continuous administration (21). Furthermore, C1-INH concentrate is a blood product and the theoretical risk of blood-borne infections cannot be excluded

completely. Nevertheless, viral (human immunodeficiency virus [HIV] or hepatitis B and C viruses) safety of the concentrate is guaranteed by heat-treatment, as well as by the establishment and continuous validation of safe plasma pools (9,22). In our series, the transmission of viral infections could not be demonstrated after the administration of C1-INH concentrate.

In pediatric patients, anti-fibrinolytic agents are the first choice for long-term prophylaxis because their safety profile is more favorable than that of attenuated androgens (3,7,8,14). Nevertheless, anti-fibrinolytic agents can cause adverse effects such as muscle weakness, myalgia, elevation of creatine kinase activity, vascular thrombosis, postural hypotension, and myonecrosis (7). Our experience shows that tranexamic acid was better tolerated than ϵ -aminocaproic acid, which often caused gastrointestinal discomfort. However, when these agents fail to achieve satisfactory improvement, treatment with attenuated androgens (e.g. danazol, stanozolol) is necessary (23). Numerous studies performed on adult patients have demonstrated the efficacy of 17 α -ethyltestosterone (danazol), manifested by the substantial relief of symptoms as well as by the elevation of serum C4 and C1-INH levels (13,24). The mechanism of action of attenuated androgens has not yet been fully elucidated and limited experience of their use in the pediatric population has been obtained in patients treated for idiopathic thrombocytopenic purpura only (25). Potential adverse effects of danazol include weight gain, myalgia, headache, tremor, libido changes, elevation of serum transaminase levels, microhematuria, menstruation irregularities, and hirsutism (26). Additionally, two reports have been published on hepatocellular adenoma formation observed in adults undergoing long-term, high-dose danazol therapy (27). Nevertheless, using the lowest effective maintenance dose and intermittent dosage regimens can prevent adverse effects that would require the withdrawal of treatment – the longest duration of danazol-prophylaxis was 11 years in our study population. No drug-related adverse reactions or impairment of growth were recorded in our pediatric patients, except for a single case of delayed menarche with subsequent irregular menstruation, which occurred probably as a result of long-term treatment with 200 mg/day of danazol. Compared to age-specific percentiles of the Hungarian population, somatomental development was normal in all cases. Treatment prevented oedematous attacks and elevated C4 and C1-INH levels significantly. Effective therapy eliminated the need for frequent hospi-

talizations because of acute symptoms – along with their unfavorable psychological sequelae – and thereby improved the patients' quality of life.

In our opinion, close follow-up is essential and appropriate tests should be performed at regular intervals. The diagnosis of hereditary angio-oedema can be made as early as at birth by assessing C1-INH antigenicity and function (11). Prenatal screening is not yet feasible. Importantly, baseline complement levels are of no use for predicting the severity and frequency of future attacks. For example, some patients are asymptomatic despite their extremely low C4 concentration and C1-INH antigenic and functional levels. Finally, when administered properly, long-term prophylaxis usually provides reliable protection against acute attacks.

During the first 2 years of long-term prophylaxis, laboratory tests should be carried out every 3–4 months and abdominal ultrasound scheduled at 6-month intervals. The clinical course of HAE and reactions to treatment should be monitored in order to recognize potential adverse effects, to ascertain the rate of somatomental development, and to assess the need for modification of therapy. In view of our favorable experience, danazol administered at the lowest effective dose seems to be well tolerated by pediatric patients and is probably appropriate for long-term therapy. Nevertheless, adverse reactions can occur sporadically. In particular, one case of delayed menarche and irregular menstruation was observed in our series; however, this abnormality is readily reversible upon discontinuation of danazol treatment.

Short-term prophylaxis is indicated for patients undergoing surgical or diagnostic interventions of the head and neck region. These interventions most commonly include dental procedures and tonsillectomy, but the importance of endotracheal intubation for general anesthesia must also be emphasized (28,29). Although short-term prophylaxis is less frequently required in children than in adults, anti-fibrinolytic agents or attenuated androgens provide adequate protection if administered in higher-than-usual doses. Nevertheless, prophylaxis with C1-INH concentrate is the method of choice in a patient with a history of severe attacks precipitated by similar procedures (30).

In addition, follow-up should also include the education of patients and their parents, as well as giving advice on the most suitable means of lifestyle modification. Self-help groups for patients can lend vigour to such efforts. Early health education and meticulous follow-up initiated in childhood can successfully prevent

social stigmatization and guarantee an improved quality of life for adulthood. It is prudent to provide HAE patients with a medical information card that summarizes essential knowledge and methods of emergency help in several languages. When justified by their history, patients should be supplied with C1-INH concentrate to be kept on hand (i.e. at home, in the refrigerator) for emergencies. The safety of patients is reinforced by the data contained by the medical information card, which can prove an extremely useful aid for medical professionals relatively unfamiliar with HAE.

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