Angioedema. Interdisciplinary diagnostic and therapeutic recommendations of the Polish Dermatological Society (PTD) and Polish Society of Allergology (PTA)

Roman J. Nowicki¹, Elżbieta Grubska-Suchanek¹, Grzegorz Porębski², Marek L Kowalski³, Karina Jahnz-Różyk⁴, Tomasz Matuszewski⁴, Lidia Rudnicka⁵, Marek Kulus⁶, Wioletta Barańska-Rybak¹, Rafał Czajkowski⁷, Zbigniew Doniec⁸, Cezary Kowalewski⁹, Beata Kręcisz¹⁰, Magdalena Lange¹, Joanna Narbutt¹¹, Małgorzata Olszewska⁵, Małgorzata Sokołowska-Wojdyło¹, Aneta Szczerkowska-Dobosz¹, Radosław Śpiewak¹², Magdalena Trzeciak¹, Aleksandra Wilkowska¹

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Abstract

Angioedema is a non-inflammatory oedema of the subcutaneous tissue and/or mucosal membranes. It most commonly coexists with urticaria wheals and is considered to be a deep form of urticaria. Less commonly, it occurs in isolation and can take two basic forms: acquired angioedema and hereditary angioedema. Currently, there are 4 defined types of acquired angioedema and 7 types of hereditary angioedema. Treatment of angioedema depends on its form and etiological factors. Especially the genetic form, i.e. hereditary angioedema, is a considerable challenge for medical specialists, particularly dermatologists and allergists.

Key words: angioedema, icatibant, ecallantide, rituximab, Berinert, Ruconest, Firazyr, Lanadelumab.

Introduction

Angioedema (AE), first described in 1882 by a German physician Heinrich Quincke (Quincke oedema), is a non-inflammatory, self-limiting type of oedema of the subcutaneous tissue and/or mucosal membranes. AE symptoms result from increased permeability of blood vessels caused by vasoactive mediators [1–4]. Oedema may coexist with urticaria or occur in isolation (without accompanying wheals) [5].

The most common manifestation of isolated AE is limited, asymmetrical skin and subcutaneous tissue swelling. The skin over the oedema is not inflamed or

itchy. The oedema usually persists for 48 to 72 h, can be limited to one site or occur at multiple sites simultaneously. It usually affects the skin of the face, mainly lips and eyelids, but can also affect the torso, limbs and genital areas. The oedema can also affect respiratory mucosa; in this form, acute pharyngolaryngeal oedema may be life-threatening. A less common and often misdiagnosed AE manifestation is gastrointestinal lesions accompanied by pain, nausea, vomiting and diarrhoea. Severe oedema at this location can imitate symptoms of acute abdomen. Particularly atypical forms of AE can be associated with

Address for correspondence: Prof. Roman J. Nowicki, Department of Dermatology, Venerology and Allergology, Medical University of Gdansk, 17 Smoluchowskiego St, 80-214 Gdansk, Poland, phone: +48 58 584 40 10, e-mail: rnowicki@gumed.edu.pl Received: 13.07.2020., accepted: 22.07.2020.

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¹Department of Dermatology, Venerology and Allergology, Medical University of Gdansk, Gdansk, Poland

²Department of Clinical and Environmental Allergology, Jagiellonian University, Clinical and Environmental Allergology Centre, University Hospital, Krakow, Poland

³Department of Immunology and Allergy, Medical University of Lodz, Lodz, Poland

⁴Department of Internal Medicine, Allergology and Clinical Immunology, Military Institute of Medicine, Warsaw, Poland

⁵Department of Dermatology, Medical University of Warsaw, Warsaw, Poland

⁶Department of Paediatric Pneumonology and Allergology, Medical University of Warsaw, Warsaw, Poland

⁷Department of Dermatology and Venereology, Ludwik Rydygier *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

⁸Department of Pneumonology, Jan and Irena Rudnik Division of the Institute of Tuberculosis and Pulmonary Diseases, Rabka, Poland

⁹Department of Dermatology and Immunodermatology, Medical University of Warsaw, Warsaw, Poland

¹⁰Dermatology Clinic, Medical and Health Science Faculty, Jan Kochanowski University, Kielce, Poland

¹¹Department of Dermatology, Paediatric and Oncological Dermatology, Medical University of Lodz, Lodz, Poland

¹²Department of Experimental Dermatology and Cosmetology, Jagiellonian University Medical College, Krakow, Poland

 Table 1. Classification of isolated angioedema (without accompanying urticaria)

Acquired (AAE)	Idiopathic	Histaminergic (AAE-IH) Non-histaminergic (AAE-InH) With C1-INH deficiency (AAE-C1-INH)		
	_			
	With known aetiology			
	_	Induced by ACE-I (AAE-ACE-I)		
Hereditary (HAE)	With C1-INH deficiency (HAE-C1-INH)	With reduced C1-INH levels, type 1 (HAE-1)		
	_	With impaired C1-INH activity, type 2 (HAE-2)		
	With normal C1-INH (HAE-nC1-INH)	With a mutation in factor XII (HAE- FXII)		
	_	With a mutation in angiopoietin (HAE-ANG)		
	_	With a mutation in plasminogen (HAE-PLG)		
	_	With a mutation in kininogen 1 (HAE-KNG1)		
		Of unknown aetiology (HAE-UNK)		

symptoms related to the urinary system, motor system and central nervous system [2, 5–10].

Isolated angioedema can assume two basic forms:

- 1) acquired angioedema (AAE) and
- 2) hereditary angioedema (HAE).

Currently, a total of 4 types of AAE and 7 types of HAE have been identified (Table 1) [6, 10–23].

Acquired angioedema (AAE)

A number of different factors may cause AAE; usually these are the same factors that trigger urticaria wheals. This type of oedema can be caused by certain drugs as well as some diseases. In some cases, available diagnostic methods are insufficient to identify the cause – this is when idiopathic oedema is diagnosed.

Types of AAE:

- 1) AAE-IH idiopathic histaminergic AAE,
- 2) AAE-InH idiopathic non-histaminergic AAE,
- 3) AAE-C1-INH AAE with C1 inhibitor deficiency,
- 4) AAE-ACE-I AAE related to ACE-I.

Idiopathic histaminergic acquired angioedema (AAE-IH)

This is one of the most common types of isolated AE. The mechanism of this type of oedema involves IgE-mediated or non-IgE-mediated mast cell activation with histamine release, and therefore it is termed "histaminergic" oedema. Similarly to urticaria, various factors may trigger this type of oedema, e.g. drugs, foods, insect venoms and other environmental allergens, as well as physical factors. AAE-IH's relation to infectious foci and autoimmune diseases is unclear. When the factor that activated mast cells cannot be identified, idiopathic oedema is diagnosed [2, 5]. The condition can occur at any age. Most commonly it is acute, sometimes chronic and recurrent. The symptoms mainly affect the face, predominantly lips and eyelids, less commonly the larynx or the gastrointestinal mucosa. Family history of AE is negative [2].

Diagnostic workup: it is important to try to identify the etiological factors responsible and any co-morbidities, and to rule out other types of AAE and HAE [2, 18].

Treatment: AHs, sometimes at multiplied daily doses, similarly as in urticaria, and in acute forms additionally glucocorticosteroids (GCS) and adrenaline [2].

Idiopathic non-histaminergic acquired angioedema (AAE-InH)

Causes and clinical presentation of this form of oedema are similar to AAE-InH, but the symptoms are not resolved with antihistamines, hence the name "non-histaminergic" oedema. The principal mediator responsible for the symptoms in AAE-InH is bradykinin, but the role of leukotrienes, prostaglandins and platelet activating factor cannot be ruled out [2]. This disease mainly affects middle-aged patients; women are affected slightly more often. Most patients exhibit facial oedema; approximately one third also develop upper respiratory and gastrointestinal symptoms. This type of oedema, as the AAE-IH, is not a familial disease [2, 20].

Diagnostic workup: same as recommended for AAE-IH. Treatment: a large number of patients respond well to tranexamic acid — a synthetic amino acid with antihemorrhagic activity. In patients with contraindications to this drug, GCS, cyclosporine A or omalizumab may be considered. The varying responses of AAE-InH patients to different therapies indicate heterogeneity of this type of oedema and participation of various mediators in its pathomechanism [2, 22, 23].

Acquired angioedema with C1 inhibitor deficiency (AAE-C1-INH)

This form of the disorder is diagnosed in patients with C1 inhibitor deficiency without a mutation in the C1-INH gene (*SERPING1*) and without a family history of oedema [2]. Reduced C1-INH levels in this type of AE may result from increased consumption of this inhibitor or from production of C1-INH-neutralizing antibodies. This is

observed in lymphoproliferative diseases, gammopathies as well as autoimmune disorders, e.g. systemic lupus erythematosus [2, 10, 24].

AAE-C1-INH occurs in adults of both sexes, usually over 40 years of age. The oedema usually affects the face, tongue, uvula and upper airways, but can also appear at any other location. Gastrointestinal symptoms are markedly less common than in hereditary angioedema with C1 inhibitor deficiency [2, 24].

Diagnostic workup: the fundamental step is detection of reduced serum C1-INH levels. In the majority of patients this parameter does not exceed 50% of normal value, although in some patients, in particular at an early stage of the disease, C1-INH abnormalities may manifest only during an oedema attack. Reduction of serum C4 and C1q levels is also typical for this form of oedema. If the clinical presentation and test results are inconclusive, identification of the *SERPING1* mutation may be necessary to confirm this diagnosis [2].

Testing for co-morbidities, e.g. lymphoreticular proliferations, monoclonal gammopathy of uncertain significance (MGUS) or autoimmune diseases is necessary in all patients diagnosed with AAE-C1-INH. The recommended laboratory tests include complete blood count with differential, C-reactive protein, serum protein electrophoresis, analysis of light chains in 24-hour urine collection. When complete blood count is abnormal, more detailed haematology tests should be performed [2, 10, 25].

Treatment: involves predominantly therapy of the potential underlying diseases. If such management is impossible or ineffective, and the oedema is severe, anti-oedema therapy should be initiated. Reduction of oedema frequency and intensity can be achieved in some patients with C1-INH supplementation, but not all patients respond to this therapy, which is due to the extremely rapid catabolism of this inhibitor. Use of a type 2 bradykinin receptor antagonist (icatibant) or plasma kallikrein inhibitor (ecallantide) may also be attempted [2, 26]. There are also reports documenting good therapeutic effects of rituximab, a monoclonal anti-CD20 antibody [27, 28]. Attenuated androgens are less effective than in hereditary oedema with C1-INH deficiency. Tranexamic acid is recommended for prophylaxis [2].

Acquired angioedema related to ACE-I therapy (AAE-ACE-I)

The pathomechanism of this disorder is due to ACE-I affecting bradykinin metabolism. Angiotensin-converting enzyme breaks down bradykinin to inactive metabolites. Inhibition of its activity by administration of ACE-I results in increased bradykinin levels and development of oedema. This disease affects approximately 0.5% of patients treated with ACE inhibitors. The development of oedema is favoured by coexistence of other factors that inhibit bradykinin catabolism [2, 29]. Concomitant use of ACE-I and other drugs, e.g. immunosup-

pressants or calcium channel blockers, increases the risk of angioedema [30]. This type of oedema usually affects patients over the age of 65, more often women. The symptoms usually develop shortly after the initiation of ACE-I therapy, although cases of onset after many years of good treatment tolerance have also been reported. The symptoms usually affect the face, mainly lips and eyelids, the neck, the tongue and upper airways; they may be mild, but fatal cases of laryngeal oedema have also been observed. Gastrointestinal symptoms are rarely reported [2].

Diagnostic workup: establishment of the relation between the oedema symptoms and intake of ACE-I.

Treatment: discontinue the drug that causes the symptoms as soon as possible. Continuing the therapy may result in marked oedema progression and the patient's death. There have been cases of persistence of the symptoms, usually in a milder form, despite discontinuation of ACE-I. This may occur in patients with a genetic defect of bradykinin metabolism or those in whom the drug revealed AAE-InH [31]. Off-label use of icatibant, a drug approved for the treatment of hereditary angioedema with C1 inhibitor deficiency, may help in the therapy of persistent, recurrent oedema [32]. Available data indicate that angiotensin receptor blockers (ARBs) are a safe alternative for patients with ACE-I hypersensitivity [33, 34].

Hereditary angioedema (HAE)

Hereditary angioedema is a genetic condition. In most patients with this disorder, the oedema is caused by reduced concentration or inactivity of C1 complement component inhibitor. (C1-INH). This defect results from a mutation in one of the two alleles of the SERPING1 gene which codes for C1-INH [2, 6]. The inhibitor is a plasma protein composed of 478 amino acids, of a total molecular weight of 105 kD, produced by monocytes and megakaryocytes in the liver. C1-INH prevents spontaneous activation of the classical complement pathway by inhibiting serine protease. It also affects activation of kallikrein and plasmin in the fibrinolytic system, as well as activation of factor XI in the clotting system and activated factor XIIa. C1-INH deficiency or impaired function results in excessive synthesis of kinin-like C2b complement component and bradykinin. Bradykinin binds to bradykinin receptor B2, causing increased blood vessel permeability and oedema.

With the progress of genetic testing, the pathomechanism of some other types of hereditary angioedema without C1-INH defect could be identified. So far there have been reports of oedemas with a mutation of the gene coding for factor XII of the clotting system, with a mutation of the gene coding for plasminogen and with a mutation of the gene coding for angiopoietin 1. The

cause of hereditary angioedema remains unknown in some patients [6, 10, 11].

Types of HAE:

- 1) with C1-INH deficiency (HAE-C1-INH):
 - a) HAE-1 due to C1-inhibitor deficiency,
 - b) HAE-2 due to C1-inhibitor dysfunction;
- 2) with normal C1-INH (HAE-nC1-INH):
 - a) HAE-FXII hereditary angioedema due to a mutation in the factor XII gene,
 - b) HAE-PLG hereditary angioedema due to a mutation in the plasminogen gene,
 - c) HAE-ANG hereditary angioedema due to a mutation in the angiopoietin 1 gene,
 - d) HAE-KNG1 hereditary angioedema due to a mutation in the kininogen-1 gene,
 - e) HAE-UNK hereditary angioedema of unknown origin.

Depending on the involvement of individual mediators in the pathomechanism, mast cell mediator-related (mainly histamine-related) and non-histaminergic forms of angioedema have been identified. The latter mainly include isolated oedema (not associated with urticaria), in particular their hereditary forms – bradykinin is a predominant mediator here (Table 2) [2, 6, 15]. Participation

of individual mediators in various types of angioedema affects both the clinical presentation of the disease and response to therapy (Table 3) [18, 19].

Hereditary angioedema with C1-INH deficiency (HAE-C1-INH)

It presents in two forms:

- a) HAE-1 related to quantitative C1 esterase inhibitor deficiency; the most common form of HAE.
- b) HAE-2 a markedly less common form with reduced activity of C1 inhibitor despite its normal concentration.

This condition is caused by a mutation in one of the two alleles of the *SERPING1* (*serpin family G member*) gene coding for C1-INH. It is an autosomal dominant condition, thus most patients have a positive family history. *De novo* mutations have been reported as the cause of the disease in approximately 20–25% of cases; in these cases, family history is negative [1, 10, 35]. Despite the fact that the gene defect has been present since birth, symptoms rarely manifest in the neonatal period or during infancy [36]. The onset usually occurs at a young age, most commonly between 5 and 11 years, but sometimes the first episode occurs in adulthood. This condition usu-

Table 2. Involvement of mediators in individual types of angioedema

With C1-INH deficiency/defect	Hereditary	HAE-1, HAE-2	
_	Acquired	AAE-C1-INH	
With normal C1-INH	Hereditary	HAE-nC1-INH	
		(HAE-FXII,	
		HAE-ANG,	
		HAE-PLG	
		HAE-KNG1	
		HAE-UNK)	
	Acquired	AAE-ACE-I	
Mediated by IgE	With anaphylaxis/urticaria		
Non-IgE-dependent	With urticaria		
	Idiopathic		
	With normal C1-INH Mediated by IgE	Acquired With normal C1-INH Hereditary Acquired Acquired Mediated by IgE With anaph Non-IgE-dependent With	

Table 3. Clinical and therapeutic differences between histaminergic and non-histaminergic angioedema

Type of angioedema			
Histaminergic	Non-histaminergic		
Sudden (minutes)	Slow (hours)		
12–24 h	48–72 h or longer		
Common	Never		
Possible	Possible		
Common	Rare		
Possible	Common		
Common	Rare		
Good effect	No effect		
	Histaminergic Sudden (minutes) 12–24 h Common Possible Common Possible Common Common		

AH – antihistamines, GCS – glucocorticosteroids.

ally manifests as the oedema of deeper skin layers and subcutaneous tissue of variable location (face, chest, limbs, genital areas). It may also affect mucosa of the throat, larynx and gastrointestinal tract. The severity of lesions is highly variable, from poorly symptomatic or asymptomatic to very severe cases with numerous lifethreatening attacks [2, 6, 10].

Oedema attacks are most commonly triggered by factors such as medical procedures, mechanical injuries, physical exertion, infections or stress. In females, the symptoms are sometimes exacerbated during puberty and pregnancy, which is due to increased oestrogen levels. Moreover, some drugs, such as oral contraceptives, hormone replacement agents or ACE-I may increase the frequency and severity of the attacks [6, 37].

Diagnostic workup: an important factor is history of recurrent angioedema episodes without urticaria wheals that do not respond to drugs conventionally used to relieve oedema, such as antihistamines, GCS or adrenaline. Patients with this form of the disease often also report laryngeal oedema and recurrent abdominal pain, often persisting for a few days. A history of ACE-I use should be ruled out and attention should be paid to other drugs and allergens that can trigger the symptoms. Checking for similar symptoms in a family member is very important since it confirms HAE with high degree of probability. Laboratory tests in this type of oedema are focused on measuring complement components – primarily the concentration and activity of C1 inhibitor and C4 component. Most commonly C1-INH activity does not exceed 30% of normal value. These tests should be performed twice with a 1-3 month interval, using different blood samples. If normal values of these parameters are obtained in a patient with a clinical suspicion of HAE-C1-INH, the test should be repeated during an oedema attack. In most patients, C4 component levels are reduced in the asymptomatic period as well, both in HAE-1 and in HAE-2 [2, 6, 10, 38].

Apart from family history, age at first onset and comorbidities, differential diagnostic workup of hereditary angioedema with C1-INH deficiency (HAE-C1-INH) and acquired angioedema (AAE-C1-INH) should include the levels of C1q component. This parameter is reduced in approximately 75% of AAE-C1-INH patients, whereas it is usually normal in HAE-C1-INH [2, 6, 38, 39]. Genetic testing (for *SERPING1* mutations) is usually required in diagnostically challenging cases, e.g. with a negative family history and late onset of symptoms, and where it is necessary to differentiate from hereditary angioedema with a normal level and activity of C1-INH [6, 10].

Treatment of patients differs depending on the disease phase. In the management of HAE-C1-INH patients, it is important to identify and eliminate factors that trigger and exacerbate symptoms, such as ACE-I or oestrogen products [2].

In an acute oedema attack, a complement component C1 inhibitor (C1-INH) should be used. This group

includes plasma-derived products: pdC1-INH (Berinert) and recombinant rhC1-INH (Ruconest). These drugs are administered intravenously, at a per kg body weight dose. Berinert is used at a dose of 20 U/kg body weight, and Ruconest at a dose of 50 U/kg body weight. If the symptoms are severe, sometimes the dose needs to be repeated [2, 10, 40].

An alternative for the substitution therapy is type 2 bradykinin receptor antagonist (Firazyr). The drug is administered subcutaneously at a fixed dose of 30 mg as a ready solution in a pre-filled syringe. Occasionally a patient requires another drug dose – it should be administered 6 h after the first injection.

In Poland, therapy with plasma-derived recombinant C1-INH products and bradykinin receptor antagonists is only reimbursed in acute, life-threatening HAE-C1-INH attacks that affect the throat, larynx or the abdominal cavity. In children, only Berinert is fully reimbursed. Ruconest is reimbursed up to the age of 13, and Firazyr is not reimbursed for paediatric patients. All drugs currently used in Poland to stop an attack are approved for self-administration at home.

Patients and/or their caretakers should undergo regular training in the correct and safe use of the drug to be able to initiate the therapy on their own as soon as the first symptoms appear. Early injection of the drug reduces the severity and shortens the duration of symptoms. All patients diagnosed with HAE should be equipped with drugs for self-use, in amounts sufficient to treat 2 attacks; they should always have them at hand.

If the above-mentioned products are not available, fresh frozen plasma can be used to treat an acute attack. Another drug effective in the treatment of acute attacks, a kallikrein blocker (ecallantide), is not available in Poland [10, 40, 41].

Chronic treatment to prevent acute oedema attacks in HAE-C1-INH patients involves long-term, continuous administration of drugs to reduce the number and severity of attacks. A decision to initiate such therapy is based mainly on the frequency, severity and location of the oedema, the effectiveness of rescue treatment in stopping the oedema and the socio-occupational situation of the patient.

The first choice in prophylactic treatment is plasmaderived C1-INH, to be administered subcutaneously every 3–4 days, or lanadelumab to be given subcutaneously every 2 weeks [2, 40, 42, 43]. Lanadelumab is a monoclonal antibody, a specific kallikrein inhibitor in the kallikrein-kinin system. Studies revealed its high and lasting efficacy in the inhibition of plasma kallikrein activity, which was associated with a significant reduction of the HAE attack frequency [40, 41].

Androgen derivatives (danazol, stanazolol) are an alternative in this long-term therapy. These products are effective in prevention of acute oedema attacks in most HAE-C1-INH patients, but their use is limited by numerous adverse effects. Moreover, these drugs cannot be

Type of AE	C1-INH levels	C1-INH activity	C4 levels	C1q levels	Other tests
HAE-1	Reduced	Reduced	Reduced	Normal	Mutation in SERPING1 gene
HAE-2	Normal/increased	Reduced	Reduced	Normal	Mutation in SERPING1 gene
HAE-FXII, HAE-ANG, HAE-PLG, HAE-KNG1	Normal	Normal	Normal	Normal	Relevant gene mutation
HAE-UNK	Normal	Normal	Normal	Normal	No detectable genetic abnormalities
AAE-C1-INH	Normal/reduced	Reduced	Reduced	Reduced	Anti-C1-INH antibodies present/absent
AAE-IH, AAE-InH, AAE-ACE-I	Normal	Normal	Normal	Normal	No detectable genetic abnormalities

Table 4. Results of laboratory tests as part of diagnostic workup of angioedema

used in children and pregnant or lactating women. The dose is selected individually for each patient. Long-term use of danazol at doses exceeding 200 mg daily is not recommended [2, 44].

Antifibrinolytic drugs (tranexamic acid) are given when other drugs are contraindicated or unavailable. These products can also be used in children. Tranexamic acid is administered orally, usually at a dose of 30–50 mg/kg body weight, in 2–3 divided doses. It is usually well tolerated. The drug should be avoided in patients with a high risk of thrombosis [2, 6, 40].

Short-term therapy to prevent the attacks should be administered in HAE-C1-INH patients before medical procedures involving mechanical compression or injuries in the oral cavity, throat and larynx, as well as procedures involving disruption of tissue integrity that can induce an attack. Plasma-derived C1-INH is the therapy of choice in these situations. This product should be used at a therapeutic dose at least 6 h before the procedure. If the inhibitor is unavailable, fresh frozen plasma should be used [2, 45].

Hereditary angioedema with normal C1-INH (HAE-nC1-INH)

This variation of isolated angioedema is diagnosed in patients with a positive family history with normal C1 inhibitor levels and activity. Four types with genetic abnormalities have been identified, and one of unknown aetiology:

- 1) HAE-FXII with a mutation in factor XII of the clotting system,
- 2) HAE-PLG with a mutation in the plasminogen gene,
- 3) HAE-ANG with a mutation in the angiopoietin 1 gene,
- 4) HAE-KNG1 with a mutation in the kininogen-1 gene, and
- 5) HAE-UNK angioedema of unknown origin, where no inducing mutation could be identified [2, 6, 10, 46, 47]. Clinical presentation, diagnostic workup and therapy of this type of oedema are identical as in HAE-C1-INH. The definite differential diagnosis requires genetic testing. If autoantibodies to C1-INH are present, plasmapheresis and use of cytotoxic drugs, androgens and

tranexamic acid may be required.

Table 4 presents typical results of laboratory tests performed as part of the diagnostic workup of each type of isolated angioedema [2, 6, 48].

Monitoring of HAE patients

Disease activity and quality of life of patients should be assessed at regular follow-up visits at specialized HAE therapy centres. Patients with unstable disease require more frequent follow-up visits. C4 levels and C1-INH levels or activity monitoring is used to monitor the therapeutic effect in HAE-1/2 and AAE-C1-INH patients.

Patients with another oedema episode involving the oral cavity and/or larynx should be hospitalized at departments able to perform expedited intubation and mechanical ventilation.

Children of parents diagnosed with HAE should be immediately tested for this disease [40].

Conflict of interest

The authors declare no conflict of interest.

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