Diagnosis of hereditary angioedema

Diagnostyka wrodzonego obrzęku naczynioruchowego

Kinga Viktória Kőhalmi[1,2], László Cervenak[2], Henriette Farkas[1,2]

[1] Hungarian Angioedema Reference Center, 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] 3rd Department of Internal Medicine, Semmelweis University, Research Laboratory, Budapest, Hungary

Summary

Hereditary angioedema (HAE) is a rare disorder characterized by acute episodes of edema formation in the subcutis and/or the submucosa. The clinical picture of the disease resembles that of histamine-mediated angioedema, nevertheless bradykinin release is involved in the pathomechanism of HAE. The diagnosis of HAE can be established from the clinical manifestations, the family history, as well as the findings of complement and genetic tests. Currently, the six types of hereditary angioedema are distinguished: types I and II of hereditary angioedema with C1-inhibitor (C1-INH) deficiency (C1-INH-HAE) and the following types of hereditary angioedema with normal C1-INH levels: hereditary angioedema caused by a mutation in the Factor XII gene (FXII-HAE), the angiopoietin-1 gene (ANGPT1-HAE), and the plasminogen gene (PLG-HAE) – and hereditary angioedema of unknown origin (U-HAE).

Current options for the laboratory diagnosis of angioedemas include means for identifying C1-INH-HAE, FXII-HAE, ANGPT1-HAE, PLG-HAE and acquired angioedema with C1-INH deficiency (C1-INH-AAE). No laboratory method is available currently for diagnosing the other types of angioedemas such as idiopathic histaminergic acquired angioedema (IH-AAE), idiopathic non-histaminergic acquired angioedema (InH-AAE), acquired angioedema related to angiotensin-converting enzyme inhibitor (ACEI-AAE), and U-HAE. These disease types can be identified only by indirect methods, i.e. by exploring medical and family history, observing the clinical manifestations and the therapeutic response, as well as by excluding the presence of C1-INH deficiency, FXII-HAE, ANGPT1-HAE, and PLG-HAE.

Keywords: *hereditary angioedema, bradykinin, diagnosis, complement testing, C1-inhibitor, genetic testing*

Streszczenie

Wrodzony obrzęk naczynioruchowy (HAE, hereditary angioedema) jest rzadkim schorzeniem charakteryzującym się występowaniem ostrych epizodów obrzęku zlokalizowanych w tkance podskórnej i/lub podśluzówkowej. Obraz kliniczny schorzenia przypomina obrzęk mediowany histaminą, jednak patomechanizm HAE jest związany z uwalnianiem bradykininy. Rozpoznanie HAE może zostać ustalone na podstawie manifestacji klinicznych, wywiadu rodzinnego, jak również badań układu dopełniacza i badań genetycznych. Obecnie rozróżnia się sześć typów wrodzonego obrzęku naczynioruchowego: typ I i II wrodzonego obrzęku naczynioruchowego z niedoboru C1 inhibitora (C1-INH-HAE) oraz następujące typy wrodzonego obrzęku naczynioruchowego z prawidłowym C1-INH: wrodzony obrzęk naczynioruchowy spowodowany mutacją w genie czynnika XII (FXII-HAE), genie angiopoetyny-1 (ANGPT1-HAE) i genie plazminogenu (PLG-HAE), a także wrodzony obrzęk naczynioruchowy o nieznanym podłożu (U-HAE). Aktualnie dostępne metody diagnostyki laboratoryjnej pozwalają na zidentyfikowanie C1-INH-HAE, FXII-HAE, ANGP1-HAE, PLG-HAE i nabytego obrzęku naczynioruchowego z niedoboru C1-INH (C1-INH-AAE). Nie ma natomiast obecnie możliwości laboratoryjnego rozpoznania innych typów obrzęków naczynioruchowych, takich jak idiopatyczny histaminozależny nabyty obrzęk naczynioruchowy (IH-AAE), idiopatyczny niezależny od histaminy nabyty obrzęk naczynioruchowy (InH-AAE) i U-HAE. Te typy obrzęku naczynioruchowego mogą zostać zidentyfikowane jedynie przy pomocy pośrednich metod, tzn. dogłębnego wywiadu medycznego i rodzinnego, obserwacji klinicznych manifestacji schorzenia i odpowiedzi na leczenie, jak również wykluczenia obecności niedoboru C1-INH, FXII-HAE, ANGPT1-HAE i PLG-HAE.

Słowa kluczowe: *wrodzony obrzęk naczynioruchowy, bradykinina, diagnostyka, badanie układu dopełniacza, C1 inhibitor, badania genetyczne*

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Adres do korespondencji / Address for correspondence
Henriette Farkas MD, PhD, DSc
Hungarian Angioedema Center,
3rd Department of Internal Medicine, Semmelweis University
H-1125 Budapest, Kútvölgyi street 4, Hungary
tel.: (+36 1) 325-1481, Fax: (+36 1) 225 3899
e-mail: farkas.henriette@med.semmelweis-univ.hu

Abbreviations:

AAE – acquired angioedema

ACEI – angiotensin-converting enzyme inhibitor

ACEI-AAE – acquired angioedema related to angiotensin-converting enzyme inhibitor

ANGPT1 – angiopoietin-1

ANGPT1-HAE – hereditary angioedema due to mutation of the angiopoietin-1 gene

C1-INH – C1-inhibitor

C1-INH-HAE – hereditary angioedema with C1-INH deficiency

C1-INH-AAE – acquired angioedema with C1-INH deficiency

ENT – ear-nose-throat specialist

FXII – coagulation factor XII

FXII-HAE – hereditary angioedema due to a mutation of the coagulation factor XII

HAE – hereditary angioedema

IH-AAE – idiopathic histaminergic acquired angioedema

InH-AAE – idiopathic non-histaminergic acquired angioedema

PLG – plasminogen

PLG-HAE – hereditary angioedema due to mutation of the plasminogen gene

U-HAE – hereditary angioedema of unknown origin

Introduction

Hereditary angioedema is a rare disorder of autosomal dominant inheritance. It is characterized by acute episodes of edema formation in the subcutis and/or the submucosa. The clinical picture of the disease resembles that of allergic angioedema; however, without urticaria. Its pathomechanism involves bradykinin release, which leads to increased vascular permeability and hence, to the onset of angioedema formation of unpredictable severity and location [1, 2]. The acute episodes of hereditary angioedema do not respond to conventional therapy with antihistamines, glucocorticoids, or epinephrine. This lack of response may assist distinguishing between histamine-mediated and non-histamine-mediated angioedemas. In this case, angioedema results from bradykinin release, and requires special therapy [3]. The genetic background of the disease may include mutations of the *SERPING-1* (C1-INH) [4], the *FXII* [5], the *angiopoietin-1* [6], or the *plasminogen* gene [7]. The prevalence of C1-INH-HAE is 1/10.000 to 1/50.000. Because the majority of medical professionals are unfamiliar with this disease, the diagnosis of which requires special tests that are not available in routine laboratory practice, patients are often diagnosed late [8]. Further, misdiagnosis is common; it results in unjustified surgery or inappropriate therapy, and may even lead to a life-threatening condition. Therefore, early diagnosis is essential and of decisive importance with regard to the prospects of the patient. The diagnosis can be established from the clinical manifestations, the family history, as well as the findings of complement and genetic tests. Currently, the following six types of hereditary angioedema are distinguished: types I and II of C1-INH-HAE; three types of hereditary angioedema with normal C1-INH levels – that is, hereditary angioedema caused by a mutation in the Factor XII gene (FXII-HAE), the angiopoietin-1 gene (ANGPT1-HAE), and the plasminogen gene (PLG-HAE) – and hereditary angioedema of unknown origin (U-HAE) [4, 6, 7].

Clinical symptoms

The clinical manifestations of the disease are similar in all six types, and consist of the recurrences of subcutaneous and/or submucosal edema. The time of onset, the location, and the severity of edematous symptoms cannot be predicted in advance, and exhibit inter- and intra-individual differences. The initial onset of symptoms is usually between 10 and 12 years of age in C1-INH-HAE [9], while in FXII-HAE, mean age at the onset of symptoms is 20 to 26 years, and it is 25 to 30 years in U-HAE. In C1-INH-HAE, the delay between the onset of the initial symptoms and diagnosis is 11.2 years on average [10]. Usually, the diagnosis is established 10 to 16 years later in FXII-HAE, and with a latency of 6 to 7 years in U-HAE [11-17].

The edematous symptoms may manifest in three different ways:

1. Subcutaneous edema may involve the upper and/or the lower extremity, the face, the lips, the neck, the torso, the abdominal region, or the genitals; it is non-pruritic; it is not accompanied by cutaneous erythema or urticaria. This form of edema is the most common in all types of HAE; however, the distribution of its location is different – for example in FXII-HAE, the majority of patients had subcutaneous edema of the face [11, 12, 15, 17].
2. Upper airway edema may occur in the mucosa of the mesopharynx (pharyngeal arcs, uvula, and the soft palate), hypopharynx, larynx, or it may involve the tongue. If (ear-nose-throat) ENT examination is not available, the following indirect signs (listed here in order of increasing severity) may aid establishing the diagnosis: sore, scratchy, itchy throat; foreign body sensation („something has stuck in my throat"); lump sensation in the throat; feeling of throat tightness; dysphagia; voice changes (high-pitched or hoarse voice, roughness of voice); resonant, „barky" cough; stridor; dyspnea; fear of suffocation; aphonia; inability to breathe, speak, or cough. Gross inspection with a spatula reveals the swelling of the mucosa of the mesopharynx (pharyngeal arcs, uvula, and the soft palate) and the tongue. When ENT examination is available, it is possible to appraise laryngeal or hypopharyngeal involvement by indirect or direct laryngoscopy [18]. In FXII-HAE, upper airway edema occurred in a smaller proportion of patients, with involvement of tongue in the first place. However, in U-HAE, edema of the tongue developed in as many as 50% of patients [11, 16, 17].
3. Submucosal edema of the gastrointestinal tract can cause colicky abdominal pain, nausea, and vomiting, post-attack watery diarrhea; occasionally, hypovolemic circulatory collapse may occur in addition. Diagnostic imaging, such as abdominal ultrasound and/or CT, MR may assist establishing the diagnosis. Imaging may depict thickening of the mucosal layer of the intestinal wall, as well as free peritoneal fluid may be present in a proportion of cases. This may be confused with acute appendicitis, or ileus, primarily [19]. In FXII-HAE, thir-

ty-five to seventy percent of patients experienced abdominal HAE attacks, while in U-HAE, abdominal edema is less common [11, 13, 15-17]. Angioedema may cause acute pancreatitis resulting from the partial or complete edematous obstruction of the Wirsungian duct [20]. Extra-abdominal manifestations may occur as vague subjective symptoms, dyspnea, and chest tightness, occasionally with cutaneous edema of the torso. This syndrome is known as the „chest episode", and may be suggestive of pleural or pericardial edema and effusion [19]. Edema of the central nervous system may cause headache, visual disturbances, aphasia, hemiplegia, and seizures [21]. Finally, much less common symptoms may also occur during angioedematous episodes, including dysphagia caused by esophageal edema, as well as kidney or lumbar muscle pain resulting from ureteral/urethral obstruction [19].

Family screening

In C1-INH-HAE, the family history is positive in 75% of cases; however, a *de novo* mutation is the underlying cause in 25%, and this makes identifying affected family members impossible [22]. Positive family history – that is, the identification of family members with edematous symptoms – assists establishing the diagnosis. Screening for symptomatic and symptom-free family members is equally important, because the time of the onset of symptoms cannot be predicted in advance. Penetrance is close to 100% in C1-INH HAE. Although the patients with other types of the disease all carry the mutation, symptoms occur in only 67 to 92% of patients with FXII-HAE, for example. Patients with U-HAE should always have a symptomatic family member – as this is a diagnostic criteria (along with the typical clinical manifestations) [4].

Asymptomatic newborns or infants with a positive family history should be screened for relevant mutations by DNA analysis (*SERPING-1, FXII, angiopoietin, and plasminogen*). In case of C1-INH deficiency, complement testing should be performed on cord blood or peripheral blood. Therefore, it is important to establish the diagnosis as early as possible, ideally before the onset of the clinical manifestations [23].

Complement tests

Establishing the diagnosis of hereditary angioedemas requires complement tests, i.e. the measurement of C1-INH concentration and functional activity, as well as of C4 levels. These tests confirm the diagnosis of C1-INH-HAE, but can only exclude its presence in the other types of the disease. If HAE with normal C1-INH function is identified, molecular genetics testing is necessary. Clinical symptoms characteristic of HAE, and complement findings of reduced C1-INH functional activity and C4 level establish the diagnosis of hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE). Two types of C1-INH-HAE are distinguished. In type I of C1-INH-HAE, both the concentration and the functional activity of the C1-inhibitor protein are reduced, along with C4 level. Type II C1-INH-HAE is characterized by reduced C4 level and a normal or even elevated C1-INH concentration. However, the C1-inhibitor protein is dysfunctional and hence, its functional activity is reduced. The complement parameters are normal in the other types of HAE (FXII-HAE, ANGPT1-HAE, PLG-HAE, and U-HAE) see Table 1. If complement testing is undertaken before the age of one year (e.g. from cord blood or peripheral blood), it may yield false positive results (e.g. reduced C1-INH level) owing to the immaturity of the complement system. Therefore, it is clearly justified to repeat complement testing after the age of one year [23, 24]. When the characteristic clinical symptoms first occur during pregnancy, the test might detect reduced complement levels, owing to the expanded plasma volume. This makes establishing the diagnosis difficult and hence, complement tests should be repeated after childbirth. Two congruent results should be obtained in all cases [25].

Although the measurement of C4 level is available from the complement tests battery even in standard clinical laboratories, the determination of C4 level is not recommended for screening purposes. Pedrosa et al. found in the pediatric population aged <1 year that the correlation between complement and genetic testing was good with regard to C1-INH and f-C1-INH, but not with C4 levels [26]. Aabom et al. reported that measuring total antigenic C4 implies a risk of overlooking C1-INH-HAE patients – normal complement C4 values do not exclude hereditary angioedema [27]. The transportation and storage of blood samples may also influence the results of complement tests. These should be performed in validated laboratories, by taking into account the inter-laboratory variation of the results. In order to improve the quality of complement laboratory analysis, a standardization committee of the International Complement Society (ICS) and the International Union of Immunological Societies (IUIS) has been formed to provide guidelines for modern complement analysis and standards for the development of international testing programs [28].

Genetic testing

In the case of C1-INH-HAE, genetics studies are not prerequisites to establishing the diagnosis, because a mutation cannot be detected in 8 to 10% of the patients. However, these tests aid the diagnosis in uncertain cases [29], and are indispensable for pre-implantation and prenatal diagnostics. *In vitro* fertilization and prenatal diagnosis (with a view to therapeutic abortion) may be considered, if a mutation has been detected in a C1-INH-HAE family. However, giving advice – or not – to terminate the pregnancy is difficult, because the severity of the disease in the offspring cannot be predicted [23]. When the family history is positive – when a mutation is carried in the family – the genetic testing of umbilical cord or peripheral blood samples is the method of choice and the quickest means to determine whether the neonate has inherited C1-INH deficiency. Genetic studies are essential in FXII-HAE, ANGPT1-HAE, and PLG-HAE, because apart from the screening for mutations, no other laboratory marker exists for the diagnosis of these disease forms. In U-HAE, a mutation cannot be detected in any of the genes mentioned in the foregoing (Table I).

Further laboratory tests that are useful for establishing the diagnosis of HAE

The diagnostic evaluation of angioedema is difficult, because no specific 'rapid test' is available for immediate diagnosis. Nevertheless, during HAE attacks, an increase in the numbers of white blood cells, and of neutrophil granulocytes, as well as the elevation of plasma D-dimer levels can be observed in patients with C1-INH deficiency. However, these laboratory parameters are non–specific [30-33].

Table I. Clinical and laboratory differential diagnosis of the different types of hereditary angioedema

	C1-INH-HAE I	C1-INH-HAE II	FXII-HAE	PLG-HAE	ANGPT1-HAE	U-HAE
Gene mutation	*SERPING-1*	*SERPING-1*	*Factor XII*	*plasminogen*	*angiopoietin-1*	?
Gender	F=M	F=M	M<F	?	?	?
C4	↓	↓	N	N	N	N
C1-INH	↓	N/↑	N	N	N	N
C1-INH activity	↓	↓	N	N	N	N

C1-INH = C1-inhibitor, C1-INH-HAE = hereditary angioedema with C1-INH deficiency, FXII-HAE = hereditary angioedema due to a mutation of the coagulation factor XII, PLG-HAE = hereditary angioedema due to a mutation of the plasminogen gene, ANGPT1-HAE = hereditary angioedema due to a mutation of the angiopoietin-1 gene, U-HAE = hereditary angioedema of unknown origin, F = female, M = male, N = normal

Recently, Zuraw et al. found that threshold-stimulated kallikrein activity distinguishes bradykinin- and histamine-mediated forms of angioedema from each other. Plasma kallikrein activity was measured by the cleavage of the fluorometric substrate Z-Phe-Arg-AMC-HCL in plasma samples stimulated *ex vivo* with submaximal doses of dextran sulphate. This method allows diagnosing hereditary angioedema (HAE) even if the level of the C1-inhibitor is normal [34].

The differential diagnosis of angioedema

Current options for the laboratory diagnosis of angioedemas include means for identifying disease types with C1-inhibitor (C1-INH) deficiency, as well as for diagnosing three special types of hereditary angioedema with normal C1-INH level – i.e. those resulting from mutation of the (Hageman) Factor XII gene (FXII-HAE), the angiopoietin 1 gene (ANGPT1-HAE), or the plasminogen gene (PLG-HAE) [4, 6, 7]. No laboratory method is available currently for diagnosing idiopathic histaminergic acquired angioedema (IH-AAE), idiopathic non-histaminergic acquired angioedema (InH-AAE), acquired angioedema related to angiotensin-converting enzyme inhibitor (ACEI-AAE), and hereditary angioedema of unknown origin (U-HAE). These disease types can be identified only by indirect methods, i.e. by exploring medical and family history, observing the clinical manifestations and the therapeutic response, as well as by excluding the presence of C1-INH deficiency, FXII-HAE, ANGPT1-HAE, and PLG-HAE (Fig. 1).

When edema of the upper airways or of the subcutis responds to conventional therapy with antihistamines, glucocorticoids, or epinephrine, the condition is regarded as a form of histamine-mediated angioedema [35]. In mastocyte-mediated forms of angioedema, symptoms related to the release of mastocyte mediators – such as urticaria, erythema, generalized pruritus, bronchospasm, globus sensation, and hypotension – are commonly observed. Edema usually ensues within minutes of the exposure, and resolves completely over 24 to 48 hours.

The culprit allergen is known in a subgroup of histamine-mediated angioedemas. In another subgroup, where the antigen causing the symptoms is unknown, angioedema may be regarded as IH-AAE.

Symptoms of acute or recurrent subcutaneous and/or upper airway edema unresponsive to treatment with antihistamines, glucocorticoids, or epinephrine, as well as recurrent abdominal symptoms (colicky abdominal pain, nausea, vomiting, post-attack watery diarrhea) caused by edema of the intestinal wall or the presence of free peritoneal fluid depicted by US/CT/MR imaging are suggestive of bradykinin-mediated angioedema.

In such cases, the initial step is to ascertain whether the patient is receiving ACEI treatment. If yes, then the diagnosis of ACEI-AAE may be established – unfortunately, this diagnosis cannot yet be confirmed by laboratory tests.

If the patient is not taking ACEIs, but nevertheless experiences recurrent episodes of subcutaneous and/or submucosal edema, the diagnosis of ACEI-AAE can be excluded, and the next step is to perform complement tests. The latter is necessary even if ACEI-AAE is diagnosed, because ACEIs are possible provoking factors also in other types of HAE. Comprehensive complement testing can distinguish among the various forms of C1-inhibitor deficiencies (such as low concentration or functional activity of the C1-inhibitor, the presence of antibodies against C4, C1q, and C1-INH).

The diagnosis of C1-inhibitor deficiency can be established based on reduced C1-INH function and C4 level. If the patient experiences recurrent episodes of subcutaneous and/or submucosal edema, the family history is positive and/or C1q level is normal, the diagnosis of hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) is established. Two types of this condition are distinguished based on the activity and the concentration of the C1-inhibitor. In type I C1-INH-HAE, both the activity and the function of C1-INH are reduced. In type II C1-INH-HAE, the concentration of C1-INH is normal or elevated, whereas the function of the C1-inhibitor protein is deficient.

However, there are cases with a negative family history and a complement screen suggestive of C1-INH-HAE. These patients may harbor a *de novo* mutation, which is identified in approx. 25% of cases with C1-INH-HAE. Diagnostic evaluation must continue when the family history is negative. Reduced C1q level indicates acquired angioedema with C1-INH deficiency (C1-INH-AAE). In such cases, the underlying disease should be identified and anti-C1-INH antibody titers measured. In type I C1-INH-AAE, lymphoproliferative, onco-hematological, or autoimmune disorders can be identified as the underlying disease, and anti-C1-INH antibodies are not detectable. In type II C1-INH-AAE, IgG, IgA, or IgM autoantibodies against C-INH can be detected in various titers and isotype distributions. Type II C1-INH-AAE is probably not an independent clinical entity, because the disorder underlying this condition can be eventually identified over years of follow-up.

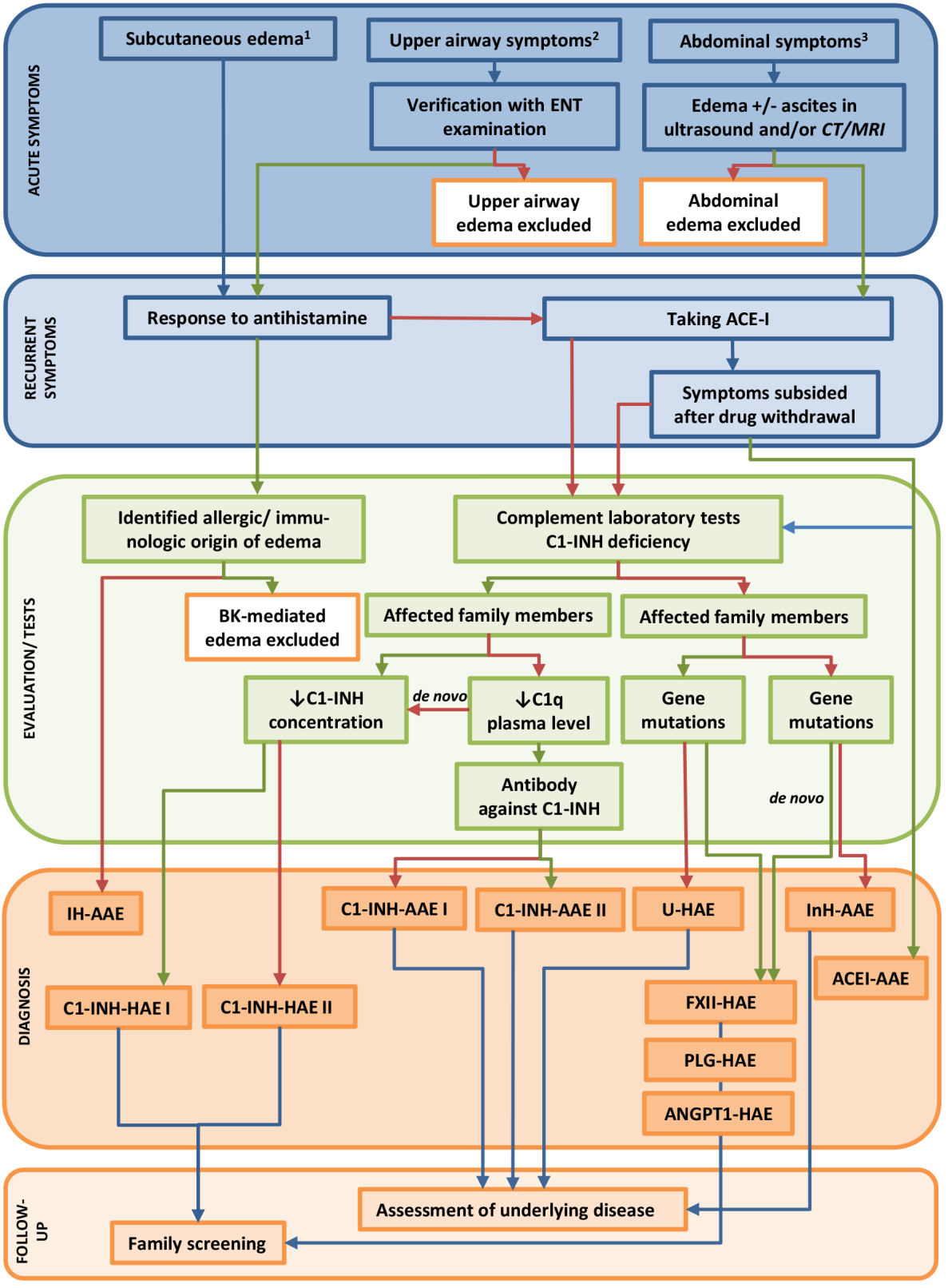

Fig.1. The differential diagnosis of angioedema.

1 edema of face, lips, trunk, extremities, urogenital area; 2 dysphagia, dyspnoe, feeling of tightness in a throat; 3 colicky pain, watery diarrhea, nausea, vomiting; green arrows = yes (presence of); red arrows = no (absence of); ENT = ear-nose-throat specialist, IH-AAE = idiopathic histaminergic acquired angioedema, ACEI-AAE = acquired angioedema related to angiotensin-converting enzyme inhibitor, C1-INH-HAE = hereditary angioedema with C1-INH deficiency, C1-INH-AAE = acquired angioedema with C1-INH deficiency, U-HAE = hereditary angioedema of unknown origin, FXII-HAE = hereditary angioedema due to a mutation of the coagulation factor XII, ANGPT1-HAE = hereditary angioedema due to mutation of the angiopoietin-1 gene, PLG-HAE = hereditary angioedema due to mutation of the plasminogen gene, InH-AAE = idiopathic non-histaminergic acquired angioedema.

When the complement tests exclude C1-INH deficiency and the family history is positive, genetic testing of the *FXII*, *angiopoietin-1*, and *plasminogen* genes should be performed in order to establish the diagnosis of FXII-HAE, ANGPT1-HAE, or PLG-HAE.

If the family history is positive, but C1-INH-HAE, FXII-HAE, ANGPT1-HAE, or PLG-HAE have been excluded, the patient has U-HAE.

When the family history is negative, the angioedema does not respond to standard therapy, and the patient is not taking ACEIs, as well as C1-INH deficiency has been excluded by complement testing, and genetic studies did not confirm mutation of the *FXII*, *ANGPT1*, and *PLG* genes, the diagnosis of InH-AAE may be established. The latter may be supported by laboratory confirmation – that is, by measuring stimulated plasma kallikrein activity, which is a potential clinical tool for the diagnosis of InH-AAE [34].

Conclusions

The clinical manifestations of bradykinin-mediated angioedemas are rather similar to those of histamine-mediated, 'allergic' angioedema. Therefore, familiarity with the steps of differential diagnosis is essential to establishing the diagnosis as early as possible – preferably before the onset of the symptoms in patients with a positive family history. Family screening is of outstanding importance in hereditary forms of angioedema. Establishing the diagnosis requires a special laboratory background capable of performing complement testing and genetic studies. Early diagnosis is essential, because the patients affected by acute episodes of HAE are often subjected to unnecessary surgery, because of misdiagnosis. Moreover, by establishing the diagnosis as early as possible, patients can be provided with appropriate therapy, which improves their quality of life, and saves them from life-threatening complications. On the other hand, the lack of appropriate treatment may be associated with the risk of life-threatening complications, such as asphyxiation in upper airway edema. The progressive advance of molecular genetics will possibly clarify the etiology also of idiopathic, and of U-HAE.

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