Original Article

Idiopathic Nonhistaminergic Acquired Angioedema Versus Hereditary Angioedema

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What is already known about this topic? The current classification of angioedema without wheals distinguishes 4 acquired and 3 hereditary forms of the disease. Idiopathic nonhistaminergic acquired angioedema (InH-AAE) and hereditary angioedema with unknown origin (U-HAE) could be difficult to diagnose.

What does this article add to our knowledge? This is the first study comparing the clinical symptoms of InH-AAE and U-HAE seen in 2 separate patient populations with those of C1-INH-HAE.

How does this study impact current management guidelines? The clinical pictures of InH-AAE and U-HAE were similar; however, these 2 disease forms were different from C1-INH-HAE, but the disease burden was similar in these 3 types of angioedema.

BACKGROUND: The mechanism of idiopathic nonhistaminergic acquired angioedema (InH-AAE) has not yet been precisely elucidated. This condition is characterized by recurrent angioedema without wheals.

OBJECTIVE: To study the clinical features of InH-AAE, and to make, for the first time, independent comparisons with hereditary angioedema of unknown origin (U-HAE), as well as with hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE).

METHODS: We compared the clinical parameters of 46 patients with InH-AAE with those of 27 patients suffering from U-HAE, as well as of 73 patients with C1-INH-HAE.

RESULTS: The mean age at the onset of symptoms was 36 years in InH-AAE, 13 years in C1-INH-HAE, and 29 years in U-HAE. More than 12 edematous episodes occurred over a year in 56% of patients with InH-AAE, in 59% of those with C1-INH-HAE, and in 48% of those with U-HAE. Edema of the extremities, of the upper airways, and of the gastrointestinal tract was more common in patients with C1-INH-HAE (92%, 51%, and 75%, respectively). These manifestations occurred less frequently in patients with InH-AAE (54%, 28%, and 20%) and in patients with U-HAE (37%, 29%, and 20%). By contrast, facial edema occurred in only 15% of patients with C1-INH-HAE, but in 67% of patients with InH-AAE and in 59% of patients with U-HAE.

CONCLUSIONS: The clinical manifestations of patients with InH-AAE were different from those of patients with C1-INH-HAE. This may indicate different processes underlying edema formation in these disease forms. The close resemblance of the clinical manifestations in InH-AAE and U-HAE might suggest a similarity between the pathophysiology of these conditions. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)

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Angioedema is nonpruritic and nonpitting swelling of the subcutaneous and/or submucosal tissues.[1] Recurrent angioedema may be accompanied by—or occur without—wheals.[2,3] Angioedema without wheals occurs in various clinical entities.[2] A form of the latter, idiopathic nonhistaminergic acquired angioedema (InH-AAE) may entail severe complications.[4,5] Nevertheless, neither its pathophysiology has been elucidated, nor its proper therapy defined. The diagnosis of InH-AAE can be established by taking a meticulous medical history, by excluding other disorders associated with angioedema of known etiology, and by ascertaining the failure of antihistamine therapy.[6] Currently, no specific laboratory parameter or test exists to establish the diagnosis of InH-AAE.[7]

The classification of angioedema without wheals distinguishes 4 acquired and 3 hereditary forms of the disease.[2] The acquired

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Abbreviations used
C1-INH-HAE- Hereditary angioedema with C1-inhibitor deficiency
FXII-HAE- Hereditary angioedema with factor XII mutation
HAE- Hereditary angioedema
InH-AAE- Idiopathic nonhistaminergic acquired angioedema
U-HAE- Hereditary angioedema of unknown origin

forms comprise acquired angioedema with C1-inhibitor deficiency, acquired angioedema related to angiotensin converting enzyme inhibitors, idiopathic histaminergic acquired angioedema, and InH-AAE—the subject of our study.[2] The most common of the 3 hereditary forms is angioedema with impaired activity or deficiency of the C1-inhibitor (C1-INH-HAE). The second, much less common form is hereditary angioedema (HAE) with mutation of the gene of the coagulation factor XII (FXII-HAE).[8,9] A proportion of patients cannot be classified into these categories, and therefore, they are identified as suffering from hereditary angioedema of unknown origin (U-HAE).[2] Very recently, novel mutations in the plasminogen (*PLG*) and in the angiopoietin 1 (*ANGPT1*) genes have been described in families previously diagnosed with U-HAE, showing that this group of HAE could contain people suffering from the same symptoms, but with different mechanism.[10,11]

The aim of our study was to explore the clinical picture of InH-AAE in a patient population that has not been subject to research so far and, therefore, has not been discussed in publications. In addition, we intended to compare the features of this disorder with those of C1-INH-HAE (a known bradykinin-mediated inherited disease) and U-HAE (another form of HAE with unknown etiology).

METHODS

Patients

In the patient population managed at the Hungarian Angioedema Center between 2009 and 2015, we diagnosed 46 patients with InH-AAE, as well as 27 patients with U-HAE (Table I). We reviewed the clinical records of these patients retrospectively. The study protocol was approved by the institutional review board of Semmelweis University of Budapest, and informed consent was obtained from the participants in accordance with the Declaration of Helsinki.

We established the diagnosis of HAE based on the recurrence of its symptoms in first- or second-degree relatives. The diagnostic evaluation of angioedema was followed by complement testing. C1-INH deficiency was diagnosed by demonstrating a C1-INH functional level less than 50% together with a low C4 level. If the patient had low C1-INH function and low C1-INH concentration, the diagnosis was HAE with C1-INH deficiency type I. If a patient had low C1-INH function with a normal or elevated C1-INH concentration, C1-INH-HAE type II was diagnosed. When C1-INH deficiency was accompanied by a negative family history and a normal C1q level, the presence of *de novo* mutations in the *SERPING1* confirmed the diagnosis of C1-INH-HAE. If the complement profile was ambiguous, mutation analysis of the *SERPING1* gene was performed in all cases. If the complement assays did not confirm C1-INH deficiency, the patients were categorized according to their family history. In case of a positive family history for angioedema, HAE with normal C1-INH function was the diagnosis.[7] Testing for mutations in the *F12* gene assisted further classification and afforded a diagnosis of FXII-HAE.[8,12] If hereditary disease forms with a known etiology could be excluded, the patients were classified into the group suffering from U-HAE.[3] The following laboratory tests were performed to identify the underlying cause of the disease: complete blood count, clinical chemistry, complement screen, thyroid hormone levels, antithyroid antibody levels, food and inhaled allergen panel (total and specific IgE), and an autoimmune battery of tests. Additional virus and postinfection serology tests, screening for possible foci of inflammation, and stool analysis were performed if necessary. When the etiology of angioedema could not be identified, a known HAE-inducing gene mutation was not found, familial clustering of the disease was missing, and antihistamine therapy with second-generation antihistamines was ineffective in preventing recurrence, the patient was diagnosed with InH-AAE.

Methods

C1-inhibitor activity was measured with a commercially available ELISA kit. Radial immunodiffusion was applied to determine C1-inhibitor concentration. C4 and C3 complement levels were determined by nephelometry. Anti-C1-INH-Ig (A, G, M) levels were quantified with an in-house ELISA method. Mutations of the *F12* gene were identified by PCR amplification followed by Sanger sequencing.[8] The antihistamine was considered ineffective when there was a lack of effect from chronic, high-dose antihistamine therapy (cetirizine at 40 mg/day or equivalent) administered over at least 1 month, possibly associated with an interval during which 3 or more attacks of angioedema occurred. The same applied to cases where conventional treatment (with antihistamines, glucocorticoids, or epinephrine, occasionally) failed to relieve the symptoms rapidly or achieved only partial relief.[7,13,14]

We compared the clinical parameters of the InH-AAE and U-HAE groups with each other, as well as with those of 73 age- and sex-matched patients with C1-INH-HAE. Different demographical data were studied. We recorded mean age at the time of the onset of symptoms/time of diagnosis and then compared these data among the 3 groups. We determined the mean number of edematous episodes occurring over a year in the studied disease forms. We analyzed the locations of the attacks reported by the subjects so far. As performing an otorhinolaryngology examination was not possible in a proportion of cases and, hence, the exact location of edema formation could not be determined, the umbrella term “upper airway edema” was used to include pharyngeal, laryngeal, and hypopharyngeal edema. In such cases, upper airway edema was suspected based on the suggestive symptoms and clinical signs (dysphagia, lump sensation in the throat, feeling of tightness, voice changes, resonant “barky” cough, stridor, dyspnea, aphony).[15,16] Furthermore, facial edema was distinguished from the swelling of the lips or tongue to map the symptoms more accurately. In patients with C1-INH-HAE, these data were available from the registry of the Hungarian Angioedema Center: the archived patient diaries contain accurate data on the frequency and location of edematous symptoms. In the other 2 study groups, these data were obtained from medical records, or from the patients themselves. On registration with the Hungarian Angioedema Center, every patient completes a standardized questionnaire on the disease symptoms experienced, and the medical history is obtained according to a standardized protocol. Previous hospitalizations are recorded accurately. The questions identify any possible familial clustering and record the medications taken by the patient along with the characteristics of the edematous episodes.

RESULTS

Symptoms first occurred in patients with InH-AAE at the age of 36 years on average. In the U-HAE group, the onset of