Original Article

Diagnosis, Course, and Management of Angioedema in Patients With Acquired C1-Inhibitor Deficiency

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What is already known about this topic? Acquired angioedema due to C1-inhibitor deficiency (C1-INH-AAE) is a rarer disease than hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE). Clinical manifestations are similar in the 2 forms; however, onset of symptoms is later, family history of angioedema is absent, and facial edema is more frequent in C1-INH-AAE.

What does this article add to our knowledge? The diagnosis of C1-INH-AAE has improved in the recent past: 35% of the patients (27 of 77) were diagnosed in the last 5 years, and patients were diagnosed earlier than expected (within 2 years of symptom development).

How does this study impact current management guidelines? Currently available treatments for acute management of C1-INH-HAE including plasma-derived C1-inhibitor concentrate, icatibant, and ecallantide (limited clinical experience) were successfully used in C1-INH-AAE; tranexamic acid was more effective than androgens for long-term prophylaxis.

BACKGROUND: Acquired angioedema due to C1-inhibitor deficiency (C1-INH-AAE) is a rare disease with no prevalence data or approved therapies.
OBJECTIVE: To report data on patients with C1-INH-AAE followed at Angioedema Center, Milan (from 1976 to 2015).
METHODS: Diagnostic criteria included history of recurrent angioedema without wheals; decreased C1-INH antigen levels and/or functional activity of C1-INH and C4 antigen less than 50% of normal; late symptom onset (>40 years); no family history of angioedema and C1-INH deficiency.
RESULTS: In total, 77 patients (58% females; median age, 70 years) were diagnosed with C1-INH-AAE and 675 patients with hereditary angioedema due to C1-INH deficiency (C1-INH-HAE) (1 patient with C1-INH-AAE/8.8 patients with C1-INH-HAE). Median age at diagnosis was 64 years. Median time between symptom onset and diagnosis was 2 years. Sixteen patients (21%) died since diagnosis, including 1 because of laryngeal edema. Angioedema of the face was most common (N = 63 [82%]), followed by abdomen (N = 51 [66%]), peripheries (N = 50 [65%]), and oral mucosa and/or glottis (N = 42 [55%]). Forty-eight of 71 patients (68%) had autoantibodies to C1-INH. In total, 56 patients (70%) used on-demand treatment for angioedema including intravenous pdC1-INH 2000 U (Berinert, CSL Behring, Marburg, Germany) (N = 49) and/or subcutaneous icatibant 30 mg (Firazyr, Shire; Milano, Italy) (N = 27). Eventually, 8 of 49 patients receiving pdC1-INH became nonresponsive; all had autoantibodies. Thirty-four patients received long-term prophylaxis with tranexamic acid (effective in 29) and 20 with androgens (effective in 8).
CONCLUSIONS: The incidence of C1-INH-AAE was 1 for every 8.8 patients with C1-INH-HAE. Thirty percent of the deaths were related to the disease. Treatments approved for C1-INH-HAE are effective in C1-INH-AAE, although with minimal differences. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Acquired angioedema; C1-INH deficiency; Prevalence; Treatment; Diagnosis*

Acquired angioedema due to C1-inhibitor (C1-INH) deficiency (C1-INH-AAE), first described in 1972, is a rare disease characterized by low levels of C1-INH, C1q, C4, and C2 and recurrent angioedema symptoms.[1] The angioedema symptoms

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Abbreviations used
ACE-I- Angiotensin-converting enzyme inhibitor
C1-INH- C1-inhibitor
C1-INH-AAE- Acquired angioedema due to C1-inhibitor deficiency
C1-INH-HAE- Hereditary angioedema due to C1-inhibitor deficiency
IQR- Interquartile range
pdC1-INH- Plasma-derived C1-inhibitor concentrate

observed in C1-INH-AAE are similar to those observed in the hereditary form of C1-INH deficiency (hereditary angioedema due to C1-inhibitor deficiency [C1-INH-HAE]), which is also a rare disease with an estimated prevalence of around 1:50,000 of the global population.[2] There are no epidemiological data on the prevalence of C1-INH-AAE in the general population, but data from limited case series suggest that it occurs less frequently than C1-INH-HAE.

In C1-INH-AAE, synthesis of the C1-INH protein is normal, but its catabolism is increased.[3] C1-INH-AAE has been described in association with various diseases, most commonly with non-Hodgkin lymphoma.[4] Other B-lymphocyte—related abnormalities, such as production of neutralizing C1-INH autoantibodies and monoclonal gammopathy of undetermined significance, are often encountered in patients with C1-INH-AAE.[5,6] These associated conditions have been demonstrated to induce C1-INH consumption and may contribute to the disease pathogenesis.[7-10] Development of C1-INH deficiency leads to activation of the contact system and consequent episodic production of bradykinin and development of angioedema, similar to that observed in C1-INH-HAE.[11]

As in C1-INH-HAE, symptoms of C1-INH-AAE include recurrent cutaneous swellings; edema of the gastrointestinal mucosa causing temporary bowel obstruction with colicky abdominal pain, vomiting, and/or diarrhea; and life-threatening laryngeal edema. Differently from C1-INH-HAE where most patients become symptomatic within the second decade of life, symptom onset occurs after the fourth decade of life in 90% of patients with C1-INH-AAE and family history of angioedema is absent.[2]

Patients with C1-INH-AAE have decreased plasma levels of C1-INH, as well as C1-INH antigen and/or C1-INH function and C4 antigen below 50% of normal. Because of deep complement consumption in the classical complement pathway, C1q is also markedly below 50%, a feature rarely present in C1-INH-HAE.[4] Furthermore, autoantibodies to C1-INH are frequently detected and may serve to confirm the diagnosis. When C1-INH autoantibodies are absent and other clinical and biochemical characteristics are not confirmatory for diagnosis, genotyping to exclude mutations in the C1-INH gene (*SERPING1*) may be necessary to rule out C1-INH-HAE.

Because clinical trials have not been performed, no therapies are specifically approved for C1-INH-AAE, although it is assumed that drugs used in C1-INH-HAE may be similarly effective in C1-INH-AAE.[12] Plasma-derived C1-INH concentrate (pdC1-INH; Berinert, CSL Behring, Marburg, Germany) and the antagonist of the bradykinin B2 receptor, icatibant (Firazyr, Shire, Milano, Italy), are used off-label to treat acute angioedema attacks of C1-INH-AAE, and tranexamic acid or androgens for long-term prophylaxis.

To improve the understanding of the landscape of C1-INH-AAE, we report data on 77 patients followed at our angioedema center in Milan.

METHODS

Patients

Patients diagnosed with C1-INH-AAE from 1976 and followed until 2015 were included in this study. Diagnosis was based on personal history of recurrent angioedema without wheals and decreased plasma levels of C1-INH antigen and/or functional activity of C1-INH and C4 antigen below 50% of normal, similar to patients with C1-INH-HAE type I/II.[13] Differently from C1-INH-HAE, all patients with C1-INH-AAE had no family history of angioedema and a later onset of symptoms (after age 40 years). When clinical and biochemical data were not confirmatory, genetic analysis was performed to exclude *SERPING1* mutation.

All patients included in the analysis gave their informed consent for using their data for the purpose of this study. Data collection and analysis were conducted by the patients' own physicians; therefore, patient confidentiality was well maintained. The study was approved by the local ethics committee.

Treatment policy

Similar to C1-INH-HAE, patients with C1-INH-AAE could avail of on-demand treatment for acute attacks at home. In Italy, this included pdC1-INH (since 1976) and icatibant (since 2010). Long-term prophylaxis was prescribed to patients with a history of more than 1 severe attack per month. The first choice for this was tranexamic acid 1 g thrice a day; for patients who had contraindications or failed to respond to tranexamic acid, danazol 200 mg once a day was prescribed. The doses of both treatments were reduced to minimal effective doses after patients became stable.

Data collection

For each patient, the following data were collected from medical records: sex, vital status (dead/alive), date of birth, date of symptom onset, date of diagnosis, plasma levels of functional and antigenic C1-INH, C4, and C1q, genetic test results (when performed), autoantibodies to C1-INH, location of angioedema attacks, on-demand therapy, and long-term prophylaxis.

Laboratory methods

Antigenic levels of C1-INH, C4, and C1q were quantified using radial immunodiffusion (NOR-Partigen, LC-Partigen; Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). C1-INH function was measured using a chromogenic assay (Technochrom C1-inhibitor, Technoclone GmbH, Vienna, Austria). Results were normalized as percentage of normal value (C1-INH function: normal range, 70%-130%; C1-INH antigen: normal range, 70%-115%; C4 antigen: normal range, 60%-140%). Autoantibodies to C1-INH were detected using a homemade modification of the ELISA described by Alsenz et al.[5,14]

Statistical analysis

Data from the C1-INH-AAE patient population were summarized with descriptive statistics and results were reported as median (interquartile range) for each parameter.

RESULTS

From 1976 until 2015, 77 patients (58% females) were diagnosed with C1-INH-AAE at our angioedema center in Milan. During the same period, 675 patients were diagnosed