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Factors associated with hospital admission in hereditary angioedema attacks: a multicenter prospective study

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ABSTRACT

Background: Acute attacks of hereditary angioedema are characterized by recurrent localized edema. These attacks can be life threatening and are associated with substantial morbidity and mortality.

Objective: To determine factors associated with hospital admission of patients with an acute attack of hereditary angioedema presenting at the emergency department.

Methods: This was a multicenter prospective observational study of consecutive patients (January 2011 through December 2013) experiencing an acute hereditary angioedema attack and presenting at the emergency department at 1 of 4 French reference centers for bradykinin-mediated angioedema. Attacks requiring hospital admission were compared with those not requiring admission.

Results: Of 57 attacks in 29 patients, 17 (30%) led to hospital admission. In multivariate analysis, laryngeal and facial involvements were associated with hospital admission (odds ratio 18.6, 95% confidence interval 3.9–88; odds ratio 7.7, 95% confidence interval 1.4–43.4, respectively). Self-injection of icatibant at home was associated with non-admission (odds ratio 0.06, 95% confidence interval 0.01–0.61). The course was favorable in all 57 cases. No upper airway management was required.

Conclusion: Most patients attended the emergency department because they were running out of medication and did not know that emergency treatment could be self-administered. Risk factors associated with hospital admission were laryngeal and facial involvement, whereas self-injection of icatibant was associated with a return home.

Introduction

Hereditary angioedema (HAE) is a rare disease. In Europe, the prevalence is 1 of 50 to 100,000 regardless of ethnicity.[1] The form with C1-inhibitor (C1-INH) deficiency is an autosomal dominant disorder, although 25% of cases with C1-INH deficiency are due to a spontaneous mutation in individuals with no family history of the disease.[2,3] Patients with decreased plasma C1-INH levels (50% below normal) but normal C1-INH activity levels (85% of patients) have type I disease. Patients with normal plasma C1-INH levels but

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Table 1
Treatments recommendations

Condition	Treatment recommendations
Severe attacks (laryngeal, face, abdominal)	as soon as possible, administer icatibant (Firazyr[a]) 30 mg subcutaneously, excpt in children and pregnant women, or C1-inhibitor concentrate (Berinert[b]) 20 IU/Kg intravenously; gain control of upper airway
Nonsevere attacks (limbs, genitals)	tranexamic acid 1 g/6 h except when breastfeeding, thromboembolic pathology
If intubation in emergency condition	C1-inhibitor concentrate (Berinert) 20 IU/kg intravenously during induction
Patients' medical contacts	systematically contact a patient's medical contact

[a]Manufactured by Shire (Lexington, Massachusetts).
[b]Manufactured by CSL Behring (King of Prussia, Pennsylvania).

low C1-INH activity levels have type II disease. Patients with a family history of the disease but a normal C1-INH level present a mutation of the gene encoding human coagulation factor XII (Hageman factor) or have HAE of unknown origin (U-HAE).[2,3] Diagnosis of U-HAE is based solely on clinical findings because plasma C1-INH levels and activity are normal and an HAE-associated mutation in factor XII gene is absent.

Acute attacks are characterized by recurrent subcutaneous swelling without itching lasting for 2 to 5 days.[2] These attacks affect the upper and lower limbs, external genital organs, and face. Painful abdominal attacks and upper airway obstruction can occur in severe cases.[3] Morbidity and mortality remain substantial, although guidelines are available for the specific treatment of acute HAE attacks.[3–5]

In a retrospective study of 457 patients with HAE in the United States, 73 (16%) presented at the hospital emergency department (ED) with an acute attack and 59% were admitted to the hospital.[6] A recent retrospective study in 193 patients with HAE in France reported a rate of approximately 8 attacks per year per patient, with approximately 11% of patients turning up at the ED or admitted to the hospital.[7] Neither of these studies described the characteristics of the attacks or the factors that might predict hospital admission. The aim of the present study was to determine the factors associated with hospital admission in patients presenting at the ED with acute HAE attacks.

Methods

Patients and Setting

This was a multicenter prospective observational study in consecutive patients who consulted the ED of each of 4 hospitals accommodating reference centers for bradykinin-mediated angioedema from January 2011 through December 2013. These centers (a network of 13 in all) were accredited in 2006 by the French Ministry of Health with the objective of improving access to diagnosis and therapy for patients with HAE. The authors approached all 13 centers in December 2010. Eight centers did not respond, 4 participated in the study (Bondy, Grenoble, Lille, and Paris), and 1 lacked a sufficiently large patient number for participation. All 4 participating centers were implementing a therapeutic education program based on guidelines for systematic treatment of severe acute attacks (abdominal, facial, or of the upper airways) and for prophylaxis of recurrent attacks, and all offered nurse-led sessions on self-administration of specific therapy for an attack.[3–5,8] Patients were encouraged to carry a rare-disease identification card giving their physician's contact details and emergency and long-term treatments. The EDs of these 4 reference centers had emergency instruction sheets on HAE management at their disposal (Table 1), enabling a service that functioned at 24 hours a day, 7 days a week, and 365 days a year.

Patients with an acute attack of angioedema presenting at the ED of 1 of the 4 reference centers were included in the study. Inclusion criteria were a documented diagnosis of HAE (type I or II, HAE with gene mutation, or U-HAE).[2,3] The diagnosis had been confirmed by a specialist in HAE based on patient history, functional and antigenic C1-INH levels, and genetic data. Exclusion criteria were a diagnosis of angioedema other than HAE (acquired angioedema with C1-INH deficiency and low C1q level, angiotensin-converting enzyme inhibitor–induced angioedema, and histamine-induced angioedema).

This study complied with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.[9] The protocol was approved by the local ethics committee (Comité de Protection des Personnes d'Ile de France 10). According to French legislation, no written informed consent was required. All patients were informed of the study plan. No opposition was voiced.

Data Collection and Analysis

For each attack, the emergency physicians prospectively collected standardized clinical data, including those laid out in the most recent Hereditary Angioedema International WorKing Group (HAWK) guidelines[2]: patient sex, age, type of angioedema, rare-disease identification card, time since diagnosis, personal history of angioedema (visits to the ED during previous year, admissions to intensive care unit, and history of intubation and of tracheotomy), ongoing long-term treatment, possible trigger of attack, reason for presentation at the ED, means of transport to the ED, day and time of onset of symptoms, day and time of arrival at the ED, edema site, self-administered home therapy, treatment administered in the ED, time treatment started, and course of attack (onset of symptom relief and time of symptom resolution). Facial edema was defined as swelling of 1 or 2 lips and/or 1 or 2 cheeks and/or 1 or 2 eyelids. Upper airway involvement was defined as laryngeal swelling and/or macroglossia.

The following times were calculated: time (in hours) before ED arrival (time of symptom onset to time of arrival), time (in minutes) before therapy (time of ED arrival to hour of icatibant or C1-INH injection), time (in hours) from attack onset to treatment start (time of symptom onset to hour of icatibant or C1-INH concentrate injection), time (in hours) to symptom relief (hour of icatibant or C1-INH concentrate injection to hour of onset of symptom relief).

Acute attacks requiring admission to the hospital were compared with those not requiring admission.

Statistical Methods

Quantitative variables are presented as medians with interquartile ranges and qualitative data are presented as numbers with percentages. Variables associated with hospital admission were identified using a logistic regression model based on generalized estimating equations because each patient could have experienced more than 1 attack. A stepwise multivariate analysis was performed with sex, age, type of attack, and treatment as candidate variables. All tests were 2-sided. A P value less than .05 was considered significant. R 2.15.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used for analysis.