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Hereditary angioedema, emergency management of attacks by a call center

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ABSTRACT

Objective: Hereditary angiœdema (HAE) is a rare autosomal dominant disease characterized by recurrent, unpredictable, potentially life-threatening swelling. Objective is to assess the management of the acute HAE attacks in the real life setting through a call center in France.

Methods: A pre-specified ancillary study of SOS-HAE, a cluster-randomized prospective multicenter trial, was conducted. HAE patients were recruited from 8 participating reference centers. The outcome of interest was the rate of hospitalization.

Results: onerhundred patients were included. The median (quartile) age was 38 (29–53) years, and 66 (66%) were female. Eighty (80%) patients had HAE type I, 8 (8%) had HAE type II and 12 (12%) patients had FXII-HAE. Fifty-one (51%) patients had experienced at least one time the call center during the follow-up. Nine over 166 (5%) attacks for 9 different patients resulted in hospital admission to the hospital (in the short-stay unit, ie, < 24 h) during the follow-up period. During 2 years, there were 166 calls to call center for 166 attacks. All attacks were treated at home after call center contact.

Conclusions: Use of emergency departments and hospitalizations are reduced by the use of a coordinated national call center in HAE after therapeutic education program that promoted self-administration of specific treatment and use of call to call center.

Trial registration: clinicalTrials.gov identifier: NCT01679912

Abbreviations: C1-INH, C1-Inhibitor; ED, Emergency department; FXII-HAE, Factor XII-hereditary angiœdema; HAE, Hereditary angiœdema; IQR, Interquartile range; SD, Standard deviation

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1. Introduction

Hereditary angiœdema (HAE) is a rare disorder with an estimated prevalence from 1/50,000 to 1/100,000 [1]. HAE type I and II are associated with SERPING1 gene mutations encoding for C1-inhibitor (C1-INH) and with C1-INH deficiency (plasma C1-INH levels below 50% of the normal values). Eighty-five percentage of patients will have low quantitative and functional plasma levels of C1-inh (type I). For patients with normal quantitative plasma levels of C1-Inh, diagnosis requires decreased C1-Inh functional levels (type II) [2,3]. Factor XII-HAE (FXII-HAE) are associated with mutation of the gene encoding human coagulation factor XII and patients have normal antigenic and functional C1-INH levels with family history of angiœdema [2,3]. Patients with HAE are characterized by spontaneous, unpredictable and recurrent edema attacks which can be potentially life threatening when the upper airway is involved (larynx and tongue). Other severe manifestations are abdominal attacks that may be painful, mimic abdominal emergencies or be associated with ascites. Severe attacks can also be edema of the face that may be disfiguring. Attacks can also affect extremities and external genital organs and are debilitating [4–6]. Treatment options are large including treatments of acute attacks, pre-procedural attack prophylaxis and long-term prophylaxis and are codified in recent guidelines [7]. However, early access to HAE specific emergency treatments is a challenge for the emergency medicine [8]. Hence, although international guidelines for management of HAE attacks exist, current management was suboptimal because emergency medical teams are often unaware of the guidelines and of new specific treatments [9–13]. In a recent study, 18 over 39 patients (46%) did not have any specific HAE treatment or received inappropriate treatment in emergency departments (ED), even though ED use is common in HAE [9]. Indeed, in a retrospective study of 193 HAE patients with 8 attacks per patient per year, approximatively 11% of patients visited the ED [14]. One strategy successfully described for other chronic disease, is to provide care support to reduce inappropriate treatment and optimize management of HAE attacks [15]. This strategy shows that a driven, targeted, population-based program can decrease hospitalizations and thereby reduce total medical costs for the targeted population as a whole [15].

The objective of the present study was to determine the management of the acute HAE attacks in the “real life setting” through a call center in France.

2. Methods

2.1. Study design

This was an ancillary study of the SOS-HAE study (NCT01679912) [16], a multicenter cluster-randomized prospective trial that assessed morbidity (number of hospital admissions) after a telephone care-management used for patients with HAE. HAE patients were prospectively recruited from eight French participating reference centers. The randomized units were the reference centers (clusters). Patients from intervention centers were assigned to receive care management through national centralization of calls made by patients during attacks. Patients from control centers were assigned to usual practice. All patients were followed for 2 years. Informed consent process was based on modified version of Zelen's method with 2-step for randomization and inclusion. Patients in usual practice group were not aware of the availability of the intervention.

From March 2013 to June 2014, for SOS-HAE study, we prospectively enrolled patients older than 18 years with documented diagnosis of HAE (type I, II or FXII). Pregnant or breastfeeding women, patients with recent history (< 1 month) of myocardial infarction or ischemic stroke were excluded (given the protective effect of bradykinin in these patients who would therefore receive bradykinin B2 receptor antagonist). Patients with allergy to icatibant or plasma-derived C1-inhibitor (C1-INH) were excluded. A 1:1 ratio randomly assigned centers (not patients) to receive intervention or usual practice. All patients in the intervention arm were given an SOS-HAE card indicating what to do in the case of severe attack. Emergency physicians receiving the call have received special training and can manage the attack.

We included for this analysis, which was planned from the start, all patients of the intervention arm of the SOS-HAE study.

3. Data collection

The complete method details can be found in the original article [16]. We collected the patients' demographic and clinical characteristics at the time of recruitment, and standardized data pertaining to their subsequent 2 years follow-up. We used clinical data in accordance with the recent Hereditary Angiœdema International Working Group Guidelines [2] and particularly data related to the current attack. For each attack, the emergency physicians prospectively collected standardized clinical data: possible trigger of attack, reason for call, day and time of onset of symptoms, day and time of call to call center, edema site, treatment availability at home, self-administered home therapy, time treatment started and course of attack (onset of symptom relief and time of symptom resolution), prehospital emergency medical service (EMS) dispatch, admission to the ED. The following times were calculated: time (in hours) before call center call (time of symptom onset to time of call), 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).

4. Outcome

The primary outcome was the rate of hospitalization.

4.1. Statistical analysis

The unit of analysis was the attack, data from the intervention group were analyzed. Descriptive statistics were used to characterize socio-demographic and clinical characteristics. Data are expressed as mean (SD) for normally distributed variables, median (interquartile range) for non-Gaussian quantitative variables, and as numbers and percentages for categorical variables. The study was approved by local ethics committee (Comité de Protection des Personnes Ile-De-France Paris X, Aulnay-sous-Bois, France).

5. Results

5.1. Characteristics of study subjects

Of the 200 patients included in the SOS AOH study, 100 could access the call center in the follow-up period of 2 years and were analyzed (Table 1). The median (quartile) age was 38 (29–53) years, and 66 (66%) were female. Eighty (80%) patients had HAE type I, 8 (8%) had HAE type II and 12 (12%) patients had FXII-HAE. Main coexisting conditions were hypertension for 11 (11%) of them, active cancer for 7 (7%), dyslipidemia for 6 (6%) and tobacco use for 5 (5%). Two patients were lost at 22 and 24 months of follow-up. Two patients died at 12 and 14 months of follow-up (due to breast cancer and leukemia, respectively). A large majority of study patients were receiving long-term prophylaxis without plasma-derived C1-INH treatment. All patients had a specific emergency treatment at home and almost all (98%) had a nurse-led formation on self-administration of specific therapy at the beginning of the trial.

6. Two-years prospective follow-up

Fifty-one (51%) patients had experienced at least one time the call

Table 1
Baseline characteristics of the study population.

Characteristics of patients of the intervention group	All patients	Call to call center	No call to call center
	N = 100	N = 51	N = 49
Demographic characteristics			
Female sex, No. (%)	66 (66)	36 (71)	30 (61)
Age, median (Q1 to Q3) years	38 (29–53)	36 (29–50)	39 (28–58)
Coexisting conditions, No. (%)			
Hypertension	11 (11)	2 (4)	9 (18)
Tobacco use	5 (5)	3 (6)	2 (4)
Diabetes	4 (4)	1 (2)	3 (6)
Dyslipidemia	6 (6)	2 (4)	4 (8)
Chronic heart failure	1 (1)	0 (0)	1 (2)
Chronic renal failure	1 (1)	0 (0)	1 (2)
Non-recent stroke	1 (1)	0 (0)	1 (2)
Cancer	7 (7)	0 (0)	7 (14)
Psychiatric disorders	0 (0)	0 (0)	0 (0)
Type of HAE, No. (%)			
HAE type I	80 (80)	42 (82)	38 (78)
HAE type II	8 (8)	3 (6)	5 (10)
FXII-HAE	12 (12)	6 (12)	6 (12)
History of angiœdema, No. (%)			
Patients with at least 1 HAE sick parents	65 (65)	39 (76)	26 (53)
Patients with at least 1 children	62 (62)	28 (55)	34 (69)
Patients with at least 1 HAE sick children	54 (54)	29 (57)	25 (51)
Patients with at least 1 HAE sick siblings	43 (43)	24 (47)	19 (39)
Years since diagnosis, median (Q1-Q3)	14 (6–29)	15 (7–30)	13 (6–27)
Long-term prophylaxis and, No. (%)			
Nurse-led formation on self-administration of specific therapy	98 (98)	51 (100)	47 (96)
Androgen	30 (30)	17 (33)	13 (27)
Tranexamic acid	16 (16)	9 (17)	7 (14)
Progestin	24 (24)	12 (24)	12 (24)
Available emergency treatment at baseline, No. (%)			
Icatibant	83 (83)	44 (86)	39 (80)
C1-INH	29 (29)	18 (35)	11 (22)

No., number of patients; HAE, Hereditary Angiœdema; FXII, HAE with mutation of the gene encoding human coagulation factor XII.

center during the follow-up. During 2 years, there were 166 calls (Table 2) to call center including 129 (78%) severe, 24 (14%) moderate and 13 (8%) mild attacks. Nine over 166 (5%) attacks for 9 different patients resulted in hospital admission to the hospital (in the short-stay unit, ie, < 24 h) during the follow-up period after 17 (10%) EMS dispatch. Call center was directly contacted by the patient in the large majority of cases (96%). Median time from symptom onset to call center call was 3.4 (1.1–7.8) hours. The site of the attacks prompting call to call center were the abdomen (86 of 166, 52%), the limbs (59 of 166, 36%), the cheeks (21 of 166, 13%), the lips (19 of 166, 11%), the upper airways (18 of 166, 11%) (including larynx, tongue and uvula) and the eyelids (4 of 166, 2%). Thirty-nine (23%) attacks were multisite. The trigger was identified for 89 (54%) attacks: stress in 55 (33%) attacks, trauma in 22 (13%) attacks, infection in 8 (5%) attacks and discontinuation of LTP in 4 (3%) attacks. All attacks were treated at home after call center contact with icatibant (30 mg subcutaneously; 93 of 166, 56%), C1-INH concentrate (20 UI/kg intravenously; 14 of 166, 8%) or tranexamic acid (1 g orally; 59 of 166, 36%). Median time from symptom onset to treatment administration was 3.4 (1.4–6.4) hours. For 17 (10%) attacks, EMS was sent home. The course was favorable for all 166 attacks with a median time from treatment to onset of symptom relief of 1.9 (0.5–11.9) hours. No invasive upper airway management (orotracheal intubation and/or tracheostomy) was required Table 3.

Table 2
Acute attacks, clinical presentation and management in patients who call the call center.

	All call	Call of HAE I/II	Call of FXII-HAE
	N = 166	N = 150	N = 16
Call center contact, No. (%)			
Own initiative	159 (96)	143 (95)	16 (100)
Family member	6 (3.5)	6 (4)	-
Friend	1 (0.5)	1 (1)	-
Trigger, No. (%)			
None	77 (46)	66 (44)	11 (69)
Stress	55 (33)	51 (34)	4 (25)
Trauma	22 (13)	21 (14)	1 (6)
Infection	8 (5)	8 (5)	-
Discontinuation of LTP	4 (3)	4 (3)	-
Site of attacks, No. (%)			
Abdominal	86 (52)	81 (54)	5 (31)
Limbs	59 (36)	56 (37)	3 (19)
Cheeks	21 (13)	15 (10)	6 (38)
Lips	19 (11)	14 (9)	5 (31)
Larynx	12 (7)	10 (7)	2 (12)
Genital	6 (4)	6 (4)	-
Eyelids	4 (2)	3 (2)	1 (6)
Tongue	4 (2)	3 (2)	1 (6)
Uvula	2 (1)	1 (1)	1 (6)
Multisite	39 (23)	36 (24)	3 (19)
Severity of attacks, No. (%)			
Mild	13 (8)	7 (5)	6 (38)
Moderate	24 (14)	22 (15)	2 (12)
Severe	129 (78)	121 (81)	8 (50)
Home therapy, No. (%)			
Self-administration before call	49 (30)	46 (31)	3 (19)
Home therapy after call, No. (%)			
Tranexamic acid	59 (36)	46 (31)	13 (81)
C1-INH	14 (8)	14 (9)	-
Icatibant	93 (56)	85 (57)	8 (50)
Home administration, No. (%)			
Patient himself	146 (88)	140 (93)	6 (38)
Health-care professional	12 (7)	10 (7)	2 (12)
Relative	8 (5)	-	8 (50)
Decision, No. (%)			
EMS dispatch	17 (10)	16 (11)	1 (6)
Admission in short-stay unit	9 (5)	8 (5)	1 (6)
Patient left on site	157 (95)	142 (95)	15 (94)
Median time, hours (IQR)			
Symptom onset to call center call	3.4 (1.1–7.8)	3.5 (1.0–7.8)	3.4 (1.2–7.9)
Symptom onset to treatment administration	3.4 (1.4–6.4)	3.4 (1.4–6.4)	3.4 (1.3–6.5)
Treatment to onset of symptom relief	1.9 (0.5–11.9)	1.9 (0.5–11.8)	1.9 (0.5–12.2)

LTP, long term prophylaxis; C1-INH, C1-inhibitor; EMS, emergency medical service; IQR, interquartile range.

7. Discussion

This first prospective study accurately describes epidemiologic characteristics of patients and the manegement of HAE attacks in France, related to call center. The hospitalization rate was small in our study. The findings suggest that HAE may lead to substantial use of call center, mainly driven by abdominal attacks and to dispatch EMS when edema attacks can be potentially life threatening. The manegement is shortened by the call center.

This cohort presents similar characteristics as those in France or others countries and some differences [14,17,18]. The predominance of female patients, the median age of patients, the rate of severe attacks and the distribution of attacks sites were similar. The median age in call center group is quite low and this is probably due that younger patients more prone to refer to the call center. It can be seen that 76% of

Table 3
Treatments recommendations for emergency physicians.

Recommendations	
Vital distress	- Immediately and as soon as possible, administer o Icatibant (Firazyr®): 30 mg subcutaneously or o Plasma-derived C1-INH (Bérinert®): 20 UI/Kg intravenously - Switch the call to the local SAMU to send French EMS - Gain control of upper airway
Severe attacks • Laryngeal • Face • Abdominal	- Immediate and as soon as possible, administer o Icatibant (Firazyr®): 30 mg subcutaneously or o Plasma-derived C1-INH (Bérinert®): 20 UI/Kg intravenously - If treatments are unavailable at home, switch the call to the local SAMU to send an ambulance headed towards a hospital with specific treatments available, or being able to get them by French EMS - Gain control of upper airway
Non-severe attacks (members, genital)	- Tranexamic acid: 1 g/6 h except for patients who are breastfeeding or have thromboembolic pathology
Surveillance in all cases	- Monitoring by phone in 30 min, 1 h, 4 h, 12 h and 24 h after the beginning of the attack - Advice to call back « SOS HAE » call center in case of secondary worsening

patients in the call center group had a HAE sick parents whereas only 56% of patients in the control group who did have a sick parent. In other words, having a sick parent seemed to make the patient aware of contactoing the call center. The predominance of emotional distress as triggering factor was similar to previous French cohort [14]. Higher rates of abdominal and limb attacks (around 60–70%) were found in previous study. Lower rates (around 5–10%) of laryngeal and face attacks were also consistent with this earlier study [19]. However, the rate of treated attacks with emergency specific drugs (icatibant or C1-INH concentrate) was higher (107/166; 64%) than in the French study (26%) [14]. This rate corresponds exactly to the total number of attacks minus the rate of limbs attacks. This was probably due to specialist advice support for management of severe hereditary angiœdema attacks and to an education program implemented by reference centers that promoted self-home treatment in accordance with recent recommendations [20]. However, tranexamic acid was used although international guidelines do not advise using antifibrinolytics for on-demand treatment of HAE attacks, as this drug show no or only minimal effects when used for on-demand treatment [7]. Further, the hospitalizations and emergency visits rate were significantly fewer in our study than those reported by Bouillet et al. [14] and previous economic study [17,18].

The most significant risk factor for EMS dispatch in this study was upper airway involvement, which affects half of HAE patients at least once during their lifetime [5]. Its incidence was similar to previous described. The relation between laryngeal edema and ED visits is known in two retrospective studies [21,22]. In this study, facial edema was never followed by laryngeal edema unlike in the retrospective study by Bork et al. [23]. This was probably because all episodes in the present study were treated by C1-INH concentrate or icatibant at home.

Median time from attack onset to call center call was fairly short (3.4 h) but this first medical contact was shorter than reported in previous prospective study [22]. Moreover, median time from call center contact to specific treatment was very short. Optimal patient management could further increase the number of immediate self-administration before call. Implementation by EMS of guideline-recommended systematic treatment of acute attacks, through use of emergency instruction sheets, yielded good results for time from first contact to treatment. Education program might increase the number of immediate self-administration treatment.

Our study has important strengths. Our sample includes a large number of HAE patients with epidemiologic data and confirmed results that have been suggested in the first SOS-HAE analysis. Of note, this study comprises one of the largest samples, one quarter of the total rare HAE population in France, of patients with epidemiologic evaluation. Hence, there is no lack of external validity and generalizations of findings may be valid since a broad population and not a selection of high-risk group was included.

8. Limitations

Potential limitations of the current study need to be considered when interpreting the data. First, as an ancillary study, it was just designed to describe epidemiologic data and no causal link could be demonstrated. Last, we included only patients who have had a follow-up into an expert HAE network, which could lead to a potential source of inclusion bias with “over-performing” HAE patients.

9. Conclusion

HAE is a rare disease whose morbidity is high with a significant impact of daily activity. Our data show that patients have frequent and severe attacks. Use of emergency departments and hospitalizations are reduced by the use of a coordinated national call center in HAE after therapeutic education program that promoted self-administration of specific treatment and use of call to call center.

Author contributions

- NJ and FA initiated and coordinated the research.
- NJ, FA, OF, EV, IDZ, LB, DL, LM, BF, AG, AS, IBG, BC and GK designed the study.
- NJ, FA, IDZ, PGR, AA, FL, EV managed and analyzed data.
- NJ, FA, AA, OF, PGR, MD, TP, AG, EV, LB, IDZ, and FL participated in the data collection and interpretation.
- NJ, FA, FL wrote the article.

All authors contributed substantially to the study and approved the final version of the article.

Conflict of interest statement

None.

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