How physicians approach hereditary angioedema: a single center study

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ABSTRACT

Background: Hereditary angioedema (HAE) is a rare autosomal dominant disorder caused by C1-inhibitor deficiency. It is characterized by recurrent attacks of cutaneous and upper respiratory tract swelling, and abdominal pain due to mucosal edema. Early detection and treatment prevent unnecessary interventions, improves quality of life, and prevents potentially fatal attacks.

Objective: The present study aims to investigate physicians level of knowledge and awareness regarding HAE.

Methods: A questionnaire about HAE was applied to 393 physicians from a university hospital. Participants were requested to choose one or several answers to multiple-choice questions.

Results: Seven and three tenths percent of study participants stated to have never heard of HAE. Twenty-seven physicians (7.4%) chose the exact correct answers regarding diagnostic tests, and 2 (0.8%) chose the exact correct answers regarding emergency management. A composite of internists, pediatrists and emergency medicine specialists had a significantly higher mean score than other physicians ($p = 0.047$). Physicians from internal medical sciences scored significantly higher than physicians from surgical medical sciences ($p = 0.022$).

Conclusion: The present study reveals that physician awareness about HAE is low, and physicians misdiagnose HAE attacks as histaminergic angioedema attacks, and therefore provide ineffective treatment. Although HAE is a rare disease, physician awareness must be increased, because early diagnosis and effective treatment are vital for the patients.

Keywords: Angioedema; Complement-C1 inhibitor protein; Disease awareness; Doctors; Hereditary angioedema

INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant disorder caused by C1-inhibitor deficiency and/or dysfunction. Estimated prevalence is 1:50 000, with various studies reporting between 1:10 000 and 1: 150 000 [1, 2]. There are 3 main types of the disease. Type I is caused by C1 esterase inhibitor deficiency, and type II is caused by C1 esterase inhibitor dysfunction. HAE type III, which is not associated with C1 esterase inhibitor deficiency or...
dysfunction, is a heterogeneous entity caused by various mutations in coagulation factor XII, angiopeptin-1 or plasminogen genes [3, 4].

HAE is characterized by recurrent attacks of subcutaneous and submucosal edema across multiple systems such as respiratory tract, skin and gastrointestinal system. Unlike histamine-mediated angioedema, skin lesions of HAE manifest as nonpruritic, nonerythematous subcutaneous swelling. Gastrointestinal submucosal edema causes colic pain, nausea and vomiting, whereas laryngeal involvement may result with life-threatening upper respiratory tract obstruction [5]. Around 2% of attacks may involve other organs and systems, including urinary bladder, urethra, central nervous system and lungs [6-9]. Attacks may persist as long as 2–7 days without treatment, and do not respond to antihistamines or steroids.

Patients often get a delayed or wrong diagnosis due to rarity of the disease and wide range of clinical presentations. Early diagnosis and correct treatment is crucial, since angioedema attacks may sometimes become life-threatening.

Multisystemic nature of HAE requires physicians across a broad spectrum of specialties to be aware of the disease. The present study aims to investigate physicians level of knowledge and awareness regarding HAE.

**MATERIALS AND METHODS**

**Participants**

The study was conducted at a university hospital. Ethics committee approval was obtained with the number of 2014-4/9. Medical doctors from each department were invited to participate in a questionnaire. Interns, residents, attending physicians and lecturers were included. Study participants were divided into 3 groups: (1) internal medical sciences (internal medicine, pediatrics, emergency medicine, infectious diseases, family medicine, psychiatry, neurology, pulmonology, physical therapy and rehabilitation, radiology, cardiology, sports medicine, forensic medicine, medical genetics, public health, child and adolescent psychiatry, dermatology), (2) surgical medical sciences (general surgery, ophthalmology, cardiovascular surgery, gynecology and obstetrics, otorhinolaryngology, urology, pediatric surgery, plastic surgery, neurosurgery, pathology, pediatric urology, anesthesiology and reanimation), (3) basic medical sciences (medical biochemistry, physiology, anatomy). Three hundred ninety-three medical doctors who completed the questionnaire were enrolled.

**Survey design**

A questionnaire was developed, and included questions regarding demographics (age, gender, years in medical practice and specialty), and physicians knowledge about HAE (symptomatology, natural history, diagnostic workup, attack triggers, management of acute attacks, and long- and short-term prophylaxis). Participants were requested to choose one or several answers to multiple-choice questions. A 'do not know' option was also offered to each question (Supplement Material 1).

**Statistical analysis**

Age was shown as mean ± standard deviation. Kolmogorov-Smirnov test was used to assess distribution of continuous variables. Categorical variables were presented as absolute and
relative frequencies. Intergroup comparisons were performed using Kruskal-Wallis and Mann-Whitney U tests. IBM SPSS Statistics ver. 20 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. A 2-sided p value of <0.05 was considered to be statistically significant.

RESULTS

Three hundred ninety-three physicians completed the questionnaire. Twenty-nine physicians who stated to have never heard of HAE were excluded. Data from remaining 364 questionnaires was analyzed. Mean age was 31.36 years (22–60 years). There were 179 women (49.2%), 185 men (50.8%), 84 interns (23.1%), 183 residents (50.3%), 44 attending physicians (12.1%), and 53 lecturers (14.6%). Two hundred thirty physicians provided information regarding their specialties (Fig. 1A–D).

Three hundred seven physicians (84.4%) were aware that HAE is characterized by recurrent attacks, and 70 (19.2%) were aware of different types of the disease.

Answers to questions about symptomatology
Five participants (1.4%) chose ‘do not know.’ Among correct answers, ‘periorbital-facial edema’ was chosen by 314 participants (86.3%), ‘tongue-lip edema’ by 303 (83.2%), ‘hand-foot edema’ by 193 (53%), ‘larynx edema’ by 222 (61%), and ‘abdominal pain’ by 124 (34.1%). Among wrong answers, ‘pruritus’ was chosen by 150 participants (41.2%), ‘urticaria’ by 125 (34.3%), and ‘fever’ by 124 (34.1%).

Answers to questions about diagnostic workup
Twenty-seven participants (7.4%) chose ‘C4 and C1 esterase inhibitor’ without choosing any wrong answers. Sixty-six participants (18.1%) chose ‘do not know’.

Answers to questions about attack triggers
Among correct answers, ‘surgery’ was chosen by 110 participants (30.2%), ‘circumcision’ by 51 (14%), ‘dental extraction’ by 86 (23.6%), ‘angiotensin converting enzyme inhibitors’ by 86 (23.6%), ‘stress’ by 162 (44.5%), ‘infections’ by 173 (47.5%), and ‘trauma’ by 109 (29.9%). Among wrong answers, ‘foods’ was chosen by 166 participants (45.6%), ‘antibiotics’ by 145 (39.8%), ‘analgesics’ by 145 (28.6%), and ‘contact with allergens’ by 211 (58%). Three participants (0.8%) chose all right answers without choosing any wrong answers.

Answers to questions about management of acute attacks, and long- and short-term prophylaxis
Wrong answers of ‘corticosteroids’ and ‘antihistamines’ were chosen by 186 (51.1%) and 184 participants (50.5%), respectively. For correct answers, see Table 1.

Participants were given 1 point for each correct answer they chose to questions about symptomatology, natural history, diagnostic workup, attack triggers, management of acute attacks, and long- and short-term prophylaxis. A maximum of 24 points could be obtained. Interns scored significantly higher than lecturers (p = 0.015). Physicians from internal medical sciences scored significantly higher than physicians from surgical medical sciences (p = 0.022). When considered as a single group, physicians from internal and basic medical sciences scored significantly higher than surgeons (p = 0.025). A composite of internists, pediatrists and emergency medicine specialists had a significantly higher mean score...
Table 1. Physicians’ approach to HAE patient management

| Subject                                                                 | No. (%)       |
|------------------------------------------------------------------------|---------------|
| Among the treatments that should be applied to the emergency patient, only those who marked all the right options | 2 (0.5)       |
| Among the treatments that should be applied to the emergency patient, those who marked at least one wrong | 362 (99.5)    |
| Total                                                                  | 364 (100)     |
| Among the treatment that should be applied to the treatment for HAE long-term prophylaxis, only those who marked all the right options | 4 (1.1)       |
| Among the treatment that should be applied to the treatment for HAE long-term prophylaxis, those who marked at least one wrong | 360 (98.9)    |
| Total                                                                  | 364 (100)     |
| Among the treatment that should be applied to the treatment for HAE short-term prophylaxis, only those who marked all the right options | 1 (0.3)       |
| Among the treatment that should be applied to the treatment for HAE short-term prophylaxis, those who marked at least one wrong | 363 (99.7)    |
| Total                                                                  | 364 (100)     |

HAE, hereditary angioedema.
than other physicians \((p = 0.047)\). There was no statistically significant difference between internists, pediatricians and emergency medicine specialists.

**DISCUSSION**

Fifty percent of patients with HAE become symptomatic in the first decade of life, and one third in the second decade. Frequency of attacks vary significantly between individuals. Thirty percent of patients experience 1 attack a month, and 40% experience 1–2 attacks a month. Remaining 30% are asymptomatic or rarely symptomatic [10]. Patients may get a delayed or wrong diagnosis due to low prevalence, wide age distribution, varying attack frequency, and broad spectrum of organ involvement.

Delay in diagnosis of HAE varies between countries. Zanichelli et al. [11] reported a diagnostic delay of 8.5 years (0–62 years) among HAE type I and II patients across 8 European countries. Time interval between onset of symptoms and a diagnosis is longer in Turkey with a reported duration of 22 ± 13.3 years [12]. This evidence shows that, like many other countries, awareness of HAE is low in our country. Despite that, there is lack of scientific studies evaluating physician awareness about HAE. Mete et al. [13] reported nearly complete awareness among a study population of 155 internists. In the present study, 29 physicians (7.3%) stated to have never heard of HAE. We believe these results from inclusion of physicians from a broad spectrum of specialties. Eighty-four percent of participants stated they had 'no opinion' regarding diagnostic tests in the study by Mete et al. [13], and 10% chose the correct answer of C1 esterase inhibitor. We confirm their finding with 27 physicians (7.4%) choosing the correct answer.

Patients who present to Emergency Departments with angioedema of the face, eyes, or lips may get ineffective treatment due to similarity of symptoms to histaminergic allergic reactions. This leads to a deterioration in quality of life. Ineffective treatment in the case of laryngeal edema may cause a threat to life. In the present study, physicians were more aware of symptoms such as 'periorbital-facial edema' and 'tongue-lip edema' 314 (86.3%) and 303 correct answers (83.2%), respectively versus symptoms of 'hand-foot edema' and 'abdominal pain' 193 (53%) and 124 correct answers (34.1%), respectively. 'Pruritus' and 'urticaria,' which are in fact symptoms of histamine-mediated angioedema, were chosen by a significant number of participants 150 (41.2%) and 125 (34.3%), respectively. These findings, supported by the result that more participants chose 'contact with allergens,' 'medications' and 'foods' versus real HAE attack triggers, suggest that physicians cannot differentiate between 2 entities of angioedema. Riedl et al. [14] reported a mean duration of 7 years between onset of symptoms and diagnosis. There is a lack of physician awareness throughout the world due to rarity of HAE.

Two physicians (0.8%) in the present study chose the exact correct answers regarding emergency management of HAE, a lower rate than reported by Mete et al. [13] 5.8% exact correct answers. The difference can be attributed to inclusion of only internists in the former study. Similar to their experience, we observed increased awareness among internists, pediatricians and emergency medicine specialists versus other physicians \((p = 0.047)\). Likewise, physicians from internal medical sciences scored significantly higher than physicians from surgical medical sciences \((p = 0.022)\).
The present study reveals that physicians across a broad spectrum of specialties cannot fully differentiate between HAE and allergic angioedema, and therefore cannot provide correct approach and treatment for these 2 entities with similar symptoms. Early diagnosis and effective treatment are crucial to improve quality of life, and prevent potentially fatal attacks. Although HAE is a rare disease, physician awareness must be increased.

SUPPLEMENTARY MATERIAL

Supplement Material 1
Questionnaire

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