How Familiar are Internists with a Potentially Deadly Orphan Disease?: Hereditary Angioedema

Ölümcül Olabilen Yetim Bir Hastalığa İç Hastalıkları Uzmanları Ne Kadar Aşina?: Herediter Anjiyoödem

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ABSTRACT Objective: Hereditary angioedema (HAE) is a rare genetic disorder characterized by episodes of swelling in the skin, gastrointestinal tract and larynx. Laryngeal attacks can be fatal, especially in mis-/undiagnosed cases. In Turkey, the mean diagnostic delay of HAE is as long as 26 years. This study was conducted to assess Turkish doctors' awareness of HAE. **Material and Methods:** A 20-question questionnaire was completed by 155 internal medicine specialists from among the attendants of 14th National Congress of Internal Medicine in Turkey. The questionnaire included HAE-related questions as well as demographic items. **Results:** Most doctors (93.5%) reported that they had heard of HAE, and 41.9% had followed at least one patient with HAE, however, 22% of them understood the role of C1 inhibitor in HAE, but 38.7% had no idea about HAE pathogenesis. The only fatal symptom, laryngeal edema, was named by 18% of respondents. Five percent of the respondents knew C4 level was the screening test; 6% knew that C1-INH level/function analysis is necessary for diagnosis. Approximately 10.3% of respondents knew an effective treatment for acute attacks; 18.7% knew a long-term prophylactic therapy. **Conclusion:** We concluded that although most internists are aware of HAE, they are not knowledgeable enough to diagnose and manage the disease.

Key Words: Angioedemas, hereditary; complement c1 inhibitor protein; physicians; internal medicine; knowledge; awareness

ÖZET Amaç: Herediter anjiyoödem (HA), deride, gastrointestinal sistemde ve larinkste tekrarlayıcı şişlik ataklarıyla seyreden nadir, genetik bir hastalıktır. Larinks atakları özellikle tanı almamış ya da hatalı tanı konmuş hastalarda ölümcül olabilmektedir. Türkiye'de HA tanısı ortalama 26 yıl kadar gecikmiş durumdadır. Bu çalışma, ülkemiz hekimlerinin HA'dan ne ölçüde haberdar olduklarını araştırmak için tasarlanmıştır. **Gereç ve Yöntemler:** 14. Ulusal İç Hastalıkları Kongresi'ne katılan 155 iç hastalıkları uzmanına bu hastalıkla ilgili 20 soru yöneltilerek hastalık hakkındaki bilgileri değerlendirilmiştir. **Bulgular:** Hekimlerin önemli bir kısmı (%93,5) HA'yı duyduğunu ve %41,9'u en az bir HA hastası takip ettiğini bildirmekle birlikte, sadece %22'si HA'da C1 inhibitörün rolünün ne olduğunu biliyor iken %38,7'si HA'nın patogenezi hakkında bir fikre sahip değildi. Hastalığın fatal semptomu olan larinks ödemi, ankete katılanların %18'i tarafından biliniyordu. Katılımcıların %5'i C4'ün tarama testi olduğunu, %6'sı C1 inhibitör düzey/işlevinin tanı için gerekli olduğunu biliyordu. Ankete katılanların %10,3'ü akut atakların tedavisinde kullanılan bir ilacın varlığından haberdar iken, %18,7'si uzun süreli profilakside ne kullanılacağı hakkında fikir sahibi idi. **Sonuç:** Bu çalışmada, iç hastalıkları uzmanlarının çoğunun bu hastalıktan haberdar olduğu, ancak bu hastalığa tanı koyma ve hastalığın tedavisini yönetme açısından yeterli bilgiye sahip olmadıkları sonucuna varılmıştır.

Anahtar Kelimeler: Anjiyoödemler, herediter; kompleman C1 inhibitör protein; doktorlar; iç hastalıkları; bilgi; farkındalık

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Hereditary angioedema (HAE) is a rare but serious genetic disorder characterized by angioedema attacks in the skin, gastrointestinal tract and upper airway that can be spontaneous or the result of var-

ious factors such as trauma.[1] HAE type I and II are the more common and better known forms of the disease. These forms result from autosomal dominant inherited C1 inhibitor (C1-INH) deficiency. Various types of mutations in the C1-INH gene result in diminished levels or function of C1-INH protein (HAE type I) or normal or elevated levels of C1-INH, which is not fully functional (HAE type II).[2] Type III is less common, and therefore not as well known. Unlike type I and II, there is no change in C1-INH level or functionality in HAE type III, yet similar symptoms are present.[3] Approximately 25% of HAE type III cases may result from mutation in the coagulation factor XII gene; however, the pathogenesis of this form of the disease is still not fully understood. Furthermore, despite the fact that most cases of type III have a family history of the disorder, the exact inheritance pattern is also unknown.[4]

The prevalence of HAE is estimated to be approximately 1 in 10 000 to 50 000 people, with no marked differences when comparing ethnic groups or gender.[5,6] The rarity of the disease, together with frequent misdiagnosis of the symptoms as allergic/anaphylactic angioedema, acute abdominal disorder or Familial Mediterranean Fever (FMF), means that while HAE symptoms often begin in early childhood and persist throughout patients' lives, awareness of the condition is extremely low and diagnosis is frequently delayed.[7-9] Failure to recognize HAE and to establish a correct diagnosis is well documented.[1,6,10,11] In a recent international survey it has been reported that patients visited an average of 4.4 different physicians for their symptoms before their condition was properly diagnosed.[10] In Turkey, the mean time between the onset of symptoms and the established diagnosis of the disease is as long as 26 years.[9] This unacceptable delay, likely attributable to doctors' relatively low level of awareness of the disease, may have serious consequences in patients' lives. The risk of death due to airway obstruction has been estimated at 30% in undiagnosed patients.[12,13] Approximately one third of patients with undiagnosed HAE may undergo unnecessary surgery during abdominal attacks, as intra-abdominal swellings are often confused with acute abdominal disorders or the situation may be mistaken for FMF due to recurrent abdominal pain.[9,14-16] Ineffective treatment can cause inadequate control of attacks, which, as a result, can affect patient's daily activities, including work or schooling.[16] In this study, we aimed to investigate the level of knowledge of HAE among internists in Turkey.

MATERIAL AND METHODS

A questionnaire consisting of 20 questions was completed on a voluntary basis by 155 internal medicine specialists from among the attendants of 14th National Congress of Internal Medicine in Turkey. The participants were all specialists in Internal Medicine and they did not know the topic of the questionnaire before agreeing to complete it. The questionnaire began with demographic items (age, gender, place of employment and years of experience) and continued with basic HAE-related questions such as, "Have you ever heard of Hereditary Angioedema?" and "Have you ever treated a patient with Hereditary Angioedema?" as well as more specific HAE-related questions such as, "What is the deficient protein in Hereditary Angioedema?"; "Does urticaria accompany Hereditary Angioedema attacks?"; "What is the cause of death in Hereditary Angioedema?"; "What are the diagnostic steps?" and "What drugs are used for prophylaxis and to treat breakthrough attacks?" This study was approved by the local ethics committee of Ege University School of Medicine and all study participants provided oral informed consent.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS for Windows 15.0 (SPSS Inc., Chicago, Ill., USA). Descriptive statistics were used to summarize demographic characteristics of the doctors. Data are presented as mean and standard deviation (SD). The relation between different parameters was examined using Pearson's x^2-test. Unpaired Student's *t*-test was used to compare mean values between different variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

The characteristics of the physicians who participated in the study were given in Table 1.

The respondents came from different medical facilities. Most of the doctors were working in state hospitals (38.7%; *n*=60), followed by training and research hospitals (21.3%; *n*=33), university hospitals (20%; *n*=31), private practice (16.1%; *n*=25), and community health centers (3.9%; *n*=6). Among these facilities, training and research hospitals and university hospitals differ from the others, as assistant training programs are available.

Of the 155 respondents, 93.5% (*n*=145) reported that they were aware of the presence of HAE, and 41.9% (*n*=65) reported that they had encountered at least one patient with HAE during their career. Awareness of HAE was more prevalent among younger doctors compared to older doctors (35.9±8.2 years vs. 45.7±13.2 years, p=0.047). There was significant difference between types of medical facilities and the proportion of doctors who had seen at least one HAE patient: Doctors practicing at university hospitals (*n*=21/31; 67.7%) were more commonly faced with HAE patients than doctors from state hospitals (*n*=25/60; 41.6%) or doctors from research and training centers (*n*=11/33; 33.3%; p=0.006)

Regarding the inheritance pattern of HAE, only 16.1% of the doctors (*n*=25) were aware that the disease had autosomal dominant inheritance pattern. Up to 38.7% of the doctors (*n*=60) reported that they had no idea about the pathogenesis of the disease, while 39.3% (*n*=61) thought that the disease was related to causes irrelevant to the pathogenesis of HAE. Only 21.9% of the doctors (*n*=34) knew that HAE is the result of C1 inhibitor deficiency. The latter group was separated by type of medical facility and the ratio of doctors who knew the role of C1 inhibitor in the pathogenesis of HAE was calculated for each group; 38.7% (12/31) of the doctors working in university hospitals knew the underlying cause of HAE, followed by doctors in state hospitals (25.0%, *n*=15/60), community health centers (16.7%, *n*=1/6), training and research hospitals (12.1%, *n*=4/33), and private practice (8.0%, *n*=2/25) (p=0.037). When compared to the other types of facilities combined, doctors working in university hospitals were significantly more familiar with this aspect of HAE pathogenesis (17.7% vs. 38.7%, respectively, p=0.014).

Sixty-two percent (*n*=96/155) of all the doctors believed that urticaria could accompany HAE attacks. When asked about diagnostic methods, only 5.2% (*n*=8) of the respondents knew that the screening test for HAE was C4 level measurement; from this group, three were from university hospitals (*n*=3/31; 9.7% of university hospitals respondents), three were from state hospitals (*n*=3/60; 5% of state hospital respondents), one was from training and research hospitals (*n*=1/33; 3% of training and research hospitals respondents), and one was from a private practice (*n*=1/25; 4% of private practice doctors). None of the doctors from community health centers knew the screening test for HAE. A percentage as small as 6% (*n*=9) reported that C1-INH levels or function had to be checked for a correct diagnosis (*n*=7: C1-INH level; *n*=1 C1-INH

TABLE 1: The demographics characteristics of the physicians according to health care centers.

	Medical Facility (n;%)					
	University Hospital n=31; 20%	State Hospital n=60; 38.7%	Training & Research Hospital n=33; 21.3%	Community Health Center n=6; 3.9%	Private Practice n=25; 16.1%	Total n=155
Gender (Female)	15; 48.4%	15; 25%	7; 21.2%	2; 33.3%	6; 24%	45; 29%
Age (Years) (mean±SD)	32.8±6.7	36.7±8.1	31.5±7.1	43±8.1	46.8±7.1	36.7±9.0
Duration of practice (Years) (mean±SD)	8.5±6.9	12.4±7.9	6.8±6.5	18.3±6.6	22.3±6.6	12.3±8.8

function; *n*=1: both C1-INH level and function) (Figure 1).

When asked about treatment options for acute attacks, 34.8% of the doctors (*n*=54) had no idea about what drugs should be used, while 54.8% (*n*=85) reported they would treat their patients with corticosteroids, adrenaline, and antihistamines and 4.5% (*n*=7) suggested treatment with FFP. Only 5.8% (*n*=9) of the doctors could name C1-INH concentrate, ecallantide and (or) icatibant as acute HAE therapies. Therapeutic approaches suggested by the doctors for acute attacks were given in Figure 2.

Regarding long-term prophylactic therapies, 29 out of 155 (18.7%) doctors suggested using C1 INH concentrate or attenuated androgens; whereas of the doctors 81.3% (*n*=126) suggested use of irrelevant medications such as CS, antihistamines, or icatibant.

DISCUSSION

The diagnostic delay experienced by HAE patients has been well documented and varies from 12.9 to 21 years in several studies.[1,8,10,11] In Turkey, the diagnostic delay is more than twice what has been reported in the most recent European survey, and is as high as 26 years.[9] Considering these data, it is clear that improvements in the diagnosis of HAE are necessary worldwide. Non-diagnosis and misdiagnosis are two of the main obstacles to improving quality of life for patients with HAE. Early detection of HAE is of key importance and can be the most important factor in reducing the risks associated with this disease. Timely and correct diagnosis of HAE can prevent avoidable deaths as well as improve patients' quality of life. Although there are more than 1800 publications worldwide about HAE, there are few if any investigations focusing on doctors' knowledge of this serious, potentially fatal disease. The current study aimed to draw attention toTurkish doctors' level of awareness of HAE. It was found that although nearly all of the doctors surveyed were aware of the existence of HAE, their knowledge of many aspects of HAE was seriously lacking.

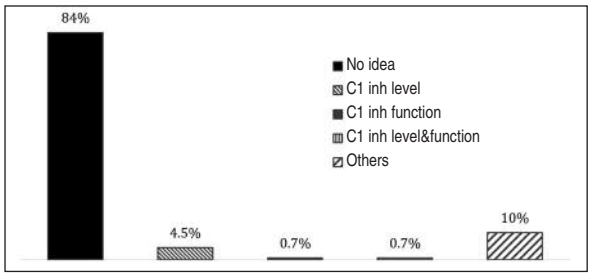

FIGURE 1: Responses regarding diagnostic evaluation. A large number of the doctors were unaware of the diagnostic approach for HAE.

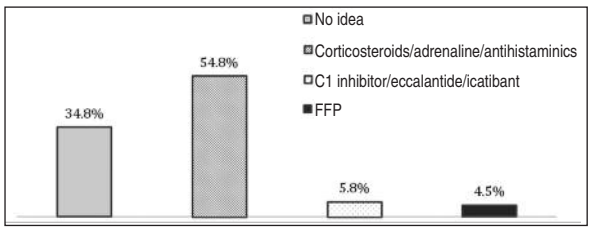

FIGURE 2: Responses regarding treatment for acute HAE attacks. Responses regarding treatment for acute HAE attacks indicate poor knowledge of therapeutic options; 5.8% of respondents could name a valid treatment for acute HAE attacks.

As the inheritance pattern of HAE is autosomal dominant, family history may offer a major clue in the diagnosis. However, only 16% of the doctors in our study were aware of the inheritance pattern of both type I and type II HAE. It is worth noting that this unawareness can itself propagate delayed diagnosis, as family screening data might be disregarded, resulting in under-diagnosis of the relatives of the index case. In a recent study it has been shown that HAE patients with a positive family history were not diagnosed earlier than those without family history (mean 12.5 years vs. 10.8 years, respectively).[10]

The wide variation of presenting symptoms can also make diagnosis challenging. Recurrent angioedema attacks are very similar to some allergic/anaphylactic reactions. Unfortunately, the laryngeal attacks occurring during an HAE attack may be mistaken for an allergic reaction; this can have serious consequences, as treatment with ineffective therapies can result in death by asphyxiation. In C1-INH dependent forms of HAE, patients usually present with cutaneous angioedema affecting various areas of the body. However, unlike mast cell mediated angioedema, as seen in allergic

conditions, urticaria is typically absent in patients with HAE.[17] This clinical clue may help physicians to distinguish mast cell mediated angioedema from bradykinin-mediated forms, as seen in HAE. However, 62% of the doctors in our study believed that urticaria could be a part of angioedema attacks. One can argue that this erroneous belief could lead to incorrect treatment with antihistamines, corticosteroids, and sometimes adrenaline as the condition itself can be mistaken for allergic conditions. In accordance with this argument, in this study, only a very small percentage of the doctors knew which drugs can be used as acute or prophylactic therapies for HAE. Fifty-four doctors (34.8%) had no idea what drugs are used to treat HAE attacks, while 85 (54.8%) reported that they would treat the patients with drugs that have no effect in HAE, such as adrenaline or antihistamines. More than 80% of the doctors did not know which drugs are used in the prophylactic therapy of HAE.

A blood test for complement C4 level between and during attacks is a very reliable test for screening HAE cases, as C4 levels are diminished in nearly all patients during attacks.[18] Blood testing for C1-INH protein level and functionality is necessary for correct diagnosis.[2,18] In the current study, only 21.9% of the doctors were aware that HAE was the result of C1-INH deficiency. Furthermore, while both C1-INH level and function analyses are necessary for a definitive diagnosis, more than 90% of the doctors did not know either of these diagnostic tests. Among doctors who were aware of HAE, the role of C1-INH dysfunction was less well known than decreased C1-INH level (Figure 1). This finding is supported by a recent study in which Zanichelli et al. reported that the mean delay between symptom onset and diagnosis was 12.2 years for type I HAE patients versus 19.6 years for type II HAE patients.[10] The underemphasis of C1-INH function analysis may be likely due to the fact that until recently it was not a standardized or widely performed test. The result is that even when HAE is suspected, patients are usually tested for only C1-INH level (and not C1-INH function), which is normal or elevated in HAE type II, misleading physicians and further delaying diagnosis.

A survey conducted in June 2010 among patient organizations representing more than 11,600 patients in 12 countries (France, Germany, Hungary, Norway, Spain, Ukraine, United Kingdom, and Israel) revealed that HAE is too often underrecognized, under-diagnosed, and under-treated by the physicians (State of management HAE in Europe. HAEi International Patient Organisation for C1-Inhibitor Deficiencies Report 2011. www.haei.org/ sites/ default/ files/ public/ 201101_ HAEi_Report.pdf). The knowledge of health professionals is rated poor or very poor by 92% of the participants. No respondent rated professional knowledge as good or very good. In the same survey, respondents estimate that across Europe, less than two fifths of patients with HAE have received a formal diagnosis. There are alarming implications for the remaining three fifths of patients who have not been diagnosed yet, given the high risk of serious and life-threatening complications associated with the disorder. In another recent international survey, patients reported having seen an average of 4.4 physicians over 8.3 years before their condition was correctly diagnosed.[19] Even after diagnosis, there have been problems with delivering effective treatment to patients in Turkey. Although C1 esterase inhibitor has been available in Europe for more than 30 years, it has only been approved in Turkey to treat HAE acute attacks since 2009 and is still not approved as a prophylactic therapy. Therefore, many Turkish HAE patients may not have continued to actively seek medical help for acute attacks after receiving a definitive diagnosis because physicians did not have effective treatments to offer to them.

Some patterns emerged regarding the doctors' knowledge of HAE. In general, younger doctors had heard of HAE more often than older doctors. Also, doctors working in university hospitals reported treating HAE patients more often than doctors working in other institutions, and also knew more about the pathogenesis of the disease. This may be explanied by the fact that an increasing number of medical schools have started to include HAE in their curriculum in recent years. This finding indicates that education about HAE is very im-

portant for doctors' awareness. The recent publication of several studies concerning HAE and new guidelines for diagnosis and treatment has increased HAE awareness among the global medical community. However, the problem of under-diagnosis is still a concern. Medical students and recent graduates seem to be benefiting from these developments, but for doctors who have not graduated recently, education about HAE needs to be incorporated into their professional development in some form.

CONCLUSION

Although nearly all of the internists in our study confirmed that they had heard of HAE, the rest of our data indicate that they are not familiar enough with the salient features of the disease to recognize it when faced with a patient with HAE. It is worth mentioning once again that physician ignorance and the resulting diagnostic delay may have irremediable and catastrophic consequences. Continuing to raise awareness of hereditary angioedema among allergists and other medical professionals is essential to ensure that patients are correctly diagnosed without delay and treated properly.

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