The diagnosis and treatment of hereditary angioedema patients in Japan: A patient reported outcome survey

Kazumasa Iwamotoa, b, m, Beverley Yamamotob, c, d, Isao Ohsawab, e, f, Daisuke Honda b, f, Takahiko Horiuchi g, Akira Tanaka h, Atsushi Fukunaga i, Junichi Maeharak, Kouhei Yamashitak, Tomoyuki Akital, Michihiro Hidea, b, *

a Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
b HAEJ Registered NPO, Japan
c Graduate School of Human Sciences, Osaka University, Osaka, Japan
d HAEJ, Registered Charity, USA
e Department of Nephrology, Internal Medicine, Saiyu Soka Hospital, Saitama, Japan
f Department of Internal Medicine, Juntendo University Faculty of Medicine, Tokyo, Japan

abstract

Background: The rate at which patients are accurately diagnosed with hereditary angioedema (HAE), as well as diagnosed patients access to modern treatments differs greatly among countries. Moreover, the severity and burden of HAE on patients have been reported mostly on the basis of physician-reported surveys. To gain insight into the real-world conditions of patients with HAE through a patient-reported survey in Japan and identify any unmet needs.

Methods: A questionnaire was distributed to 121 patients with HAE via a Japanese HAE patient organization during 2016–2017. Responses were collected from 70 patients (57.9%) and subjected to analysis.

Results: The average periods from the initial appearance of symptoms (e.g. edema) to a HAE diagnosis was 15.6 years (min: max, 0–53). Patients visited an average of 4.6 different departments until receiving definitive diagnosis. The average age at the first visit was 25.6 years (3–73) and at diagnosis 32.8 years (0–73). Patients reported an average of 15.7 (0–100) attacks per year, but only 53.1% of attacks were treated. The days of hospitalization due to severe attacks was 14.3 (0–200) before diagnosis, but these declined to 4.3 (0–50) after diagnosis. In the treatment for attacks, 82% of the patients were treated with the plasma-derived C1 inhibitor concentrate, and 69% of the patients reported experiencing a therapeutic effect.

Conclusions: There is a long gap between first attack and diagnosis of HAE, and the number of non-treated attacks is high in Japan. Steps are needed to improve the diagnostic and treatment environments to address these issues.

Introduction

Hereditary angioedema (HAE) is a genetic disorder that results in the unregulated increase of bradykinin leading to edema. It is classified into HAE type I, HAE type II and HAE with normal C1-inhibitor (C1–INH) based on serum levels of C1–INH protein and function.1 With a small but growing number of patients...
diagnosed with HAE with normal C1–INH, most patient with HAE are classified as type I, deficiency of C1–INH in both protein amount and the function, or type II, deficiency of functional C1–INH with a normal amount of protein. Both HAE type I and HAE type II are caused by a mutation in the gene for C1–INH (SERPING1) and cause unforeseen edema in the skin and mucosa, such as that in gastrointestinal tract and airway. Early diagnosis of HAE and setting up adequately individualized treatments for acute attacks and prophylaxis is important, because attacks may develop to life-threatening airway obstruction or severely impair the daily activities of the patients. In fact, at least two recent cases of fatal HAE airway attacks in Japanese young males have been reported.2,3

HAE is reported to be present in approximately 1 in 50,000, although this figure may vary by region. In Japan, the first nationwide survey of HAE was conducted in 2009 and data on 52 patients with HAE type I or II were reported.4 Since then, the number of cases reported in the literature has been increasing to date. In 2014, Ohsawa et al. reported the clinical symptoms of 171 patients collected from 94 physicians in Japan by a questionnaire instrument consisting of 14 items.5 This study revealed that mean time from initial symptoms to diagnosis was 13.8 years, that attacks with airway management and abdominal surgery with uncertain diagnosis were observed in 9.5% and 2.9% of patients, respectively. In addition, 21.0% of patients presented with more than 10 attacks per year, 21.1% were admitted to the hospital for more than 1 day, and 28.7% were absent from work or school.

Such physician-reported surveys gave us important data from a large number of patients, but the viewpoints offered were partial in terms of offering us a view of the disease burden on patients as not all events of HAE may be reported to physicians. Therefore, we performed a survey directly asking patients with HAE using a newly developed questionnaire instrument focusing on both medical management and the burden of the disease on the life of patients. In this paper, we report on the medical aspects of the analysis from that in gastrointestinal tract and airway. Early diagnosis of HAE and setting up adequately individualized treatments for acute attacks and prophylaxis is important, because attacks may develop to life-threatening airway obstruction or severely impair the daily activities of the patients. In fact, at least two recent cases of fatal HAE airway attacks in Japanese young males have been reported.2,3

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At the time of this survey, only one modern treatment was available for HAE treatment in Japan and that was a plasma-derived C1–INH concentrate (pC1-INH), Berinert®, licensed for acute attack. In the first quarter of 2017, the license for Berinert® was extended to include short-term prophylaxis. In addition, in the third quarter of 2018, icatibant, a bradykinin B2 receptor antagonist, was licensed for acute attack treatment. Our data was collected just prior to these changes. Therefore, it should be noted that the results of this survey offer a picture on unmet need prior to the licensing of Berinert®, for short-term prophylaxis and the introduction of a self-administered acute attack treatment. As such, it offers an important baseline against which future studies can investigate the impact of these improvements in HAE treatment options.

Methods

This survey collected data from patients with HAE during 2016–2017. A questionnaire instrument was prepared based on discussion with treating physicians and patients with HAE to generate knowledge to inform of practical management of the condition, to better understand the burden on the patients and unmet needs. In total, 48 questions were selected so as collect essential information without overburdening patients (Supplementary Table 1). The questionnaire was distributed via a Japanese HAE patient organization (NPO HAEJ, https://haej.org) to 121 patients between July and November in 2016, then analyzed in 2017. After filling the questionnaire at home, patients sent it back in a pre-prepared envelope to Anterio Co., Ltd., a specialized institute for pharmaceutical market research (https://www.intage-healthcare.co.jp). The data from the returned questionnaires were compiled by Anterio Co., Ltd. After removing invalid answers in each questionnaire, data were statistically analyzed using GraphPad Prism® (GraphPad Software, San Diego, CA). Statistical significance between before and after diagnosis is calculated by the Wilcoxon matched-pairs signed rank test.

For variable cluster analysis, the following questions were excluded from the analysis; (a) Questions with a response rate of less than 70% (n = 48 or less respondents), (b) Questions to which only one respondent indicated that the item was “Applicable” and the other respondents chose “Not applicable” and (c) Free description questions. The median value was used for binary categorization for Questions where the answer format was numeric. If there was a missing value in the response, the missing value was complemented by substituting the conditional expected value calculated from the non-missing value of each row. In order to examine the relevance of each variable, variable cluster analysis (hierarchical type) using all 41 variables was performed. The statistical analysis was performed by JMP Pro14 (SAS Institute, Cary, NC). This study was approved by the ethics committee of Hiroshima University (No. E–339) and performed in accordance with the Declaration of the Helsinki principles. Informed consent was obtained from all participants in this study.

Results

Sample number and patient’s background

In total, 70 (15 males, 55 females) out of 121 patients (57.9%) returned the questionnaire. The average age was 44.9 ± 18.8 years (mean ± SD, min–max, 8–84 years).

The age of onset of HAE, first visit and diagnosis

The age of initial symptoms of HAE was 18.0 ± 11.9 years (mean ± SD, median 15 years (0–60), n = 55). The age of first visit to a medical institution due to symptoms of HAE was 25.6 ± 15.8 years (median 21 years (3–73), n = 53) and the age of first diagnosis of HAE was 32.8 ± 16.2 years (median 32 years (0–73), n = 62) (Fig. 1). The average periods from the initial appearance of symptoms (e.g. edema) to the first visit to a medical facility was 5.4 ± 10.3 years (median 0 years (0–53), n = 49). The average period from the first visit to diagnosis of HAE was 9.7 ± 10.3 years (median 7.5 years (0–36), n = 52). In total, it took 15.6 ± 13.3 years (median 15 years (0–53), n = 53) from onset to diagnosis. Seven patients who had been diagnosed, but still had not had a first attack were excluded from the analysis concerned with attack and treatment history. Classified by age, the average period from initial symptom to diagnosis was 23.3 ± 15.6 years in old generation (birth before 1960), which was shorten to 9.0 ± 8.3 years in younger generation (birth after 1980).

First symptoms and medical treatment until diagnosis

Symptoms that patients have ever-experienced were (visible) swelling (n = 42/62, 68%). Among these, the first symptoms recognized by most patients were swelling (n = 50/62, 81%),
followed by abdominal pain (n = 34/62, 55%) and nausea/vomiting (n = 25/62, 40%) (Supplementary Fig. 1a, First attack). Notably, as many as 27 (44%) and 25 (40%) out of 62 patients have experienced dyspnea and breathlessness. The rate of patients reporting having ever-experienced swelling in the throat or neck is 3–4 times higher than those reporting these locations as the site of a first attack. We can see from this that after initial onset of symptoms, a laryngeal attack becomes more likely for many patients (Supplementary Fig. 1b, Ever experienced). The most frequently reported sites of swelling for having ever-experienced were the extremities, fingers and wrists (n = 28/48, 58%), feet and ankles (n = 19/48, 40%), and the face (n = 14/48, 29%) (Supplementary Fig. 1b, First attack). Swelling of these sites were then experienced by around 80% patients (Supplementary Fig. 1b, Ever experienced).

The medical department most frequently visited for the first time in connection with HAE symptoms was general medicine (n = 26/47, 55%), followed by dermatology (n = 7/47, 15%) (Supplementary Fig. 2a, First visit). A breakdown of medical departments that patients visited before diagnosis included general medicine (n = 41/54, 76%), gastroenterological medicine (n = 24/54, 44%), and dermatology (n = 19/54, 35%) (Supplementary Fig. 2a, Total visit). Patients who developed gastroenterological symptoms showed a weak tendency to visit gastroenterology (n = 3/47, 6.4%) or general internal medicine (n = 2/47, 4.3%). On the other hand, most patients with only skin-located symptoms consulted general internal medicine (n = 10/47, 21.3%) or dermatology (n = 5/47, 10.6%) (Supplementary Fig. 2b).

Only 12% (n = 8/63) patients were diagnosed with HAE at the first medical institution that they visited, and patients presented their symptoms to an average of 4.6 ± 4.6 different areas of specialty (mean ± SD, median 4.0, n = 52) before the diagnosis of HAE was made (Supplementary Fig. 2c). As many as 92.2% (n = 47/51) of patients had blood tests, but only 32.4% (n = 11/34) of the patients received genetic testing (Supplementary Fig. 3a). Family screening for HAE by gene analysis was performed for all relatives in 26.9% (n = 18/67) cases, and for some relatives in 62.7% (n = 42/67) cases (Supplementary Fig. 3b).

Before final diagnosis with HAE, patients were given various alternative diagnoses to explain their symptoms. The most frequent diagnosis was gastroenteritis/enteritis (n = 21/44, 48%), followed by appendicitis (n = 11/44, 25%), allergy (n = 9/44, 21%) and (non-hereditary) angioedema (n = 8/44, 18%) (Supplementary Fig. 4a). Accordingly, digestive drugs (n = 14/38, 37%), allergic drugs (n = 9/38, 24%), steroids (n = 6/44, 16%), antibiotics (n = 5/44, 13%) and analgesics (n = 5/44, 13%) were prescribed in many cases (Supplementary Fig. 4b).

Number of attacks and treatments

The average number of attacks per year was 15.7 ± 26.4 (mean ± SD, median 5.0, n = 61) (Fig. 2a). Patients were classified into a high frequency group with 20 or more attacks per year (n = 18/69, 26.1%), a low frequency group with 1–19 attacks per year (n = 28/69, 40.6%), a no attack group reporting no attacks in the previous year but a history of attacks (n = 7/69, 11.6%), an asymptomatic group that had never had an attack (n = 7/69, 10.1%) and an unknown group who did not indicate the number of attacks (n = 8/69, 11.6%) (Fig. 2b). In total 960 HAE attacks were recorded of which, 510 attacks (53.1%) were treated and the other 450 attacks (46.9%) were not treated (Fig. 2c). Among 46 patients who had experienced attacks in the last year, only 15 (32.6%) patients received treatment for all attacks, and 7 (15.2%) patients did not treat any attacks (Fig. 2a).

Days of hospitalized and absent from work/school in one year

The number of days hospitalized per year before being diagnosed with HAE was 14.3 ± 5.3 days (mean ± SEM, median 3.3 days, n = 46), and significantly decreased to 4.3 ± 1.3 days (median 0 days, n = 46) after the diagnosis (p = 0.0074). However, as many as 19 out of 46 (41.3%) patients still needed to be hospitalized even after the diagnosis for a day or longer (Fig. 3a). The absenteeism from work or school was 17.5 ± 4.4 days (mean ± SEM, median 10.0 days, n = 38) before being diagnosed with HAE, and shortened to 10.2 ± 3.6 days (median 3.0 days, n = 46) after diagnosis (p = 0.0044) (Fig. 3b).

Attack treatment time and treatment effect

For the treatment for acute attacks, pdC1-INH was the most commonly prescribed medication (n = 51/62, 82.3%), followed by oral tranexamic acid (antifibrinolytic agent; n = 14/62, 22.6%), tranexamic acid injections (n = 12/62, 19.4%) and danazol (androgen; n = 4/62, 6.5%) (Fig. 4a). Approximately 70% of patients recognized these medications as very effective (n = 21/62, 33.9%) or effective (n = 22/62, 35.5%) for improving symptoms developed in attacks (Fig. 4b). Since none of the modern medications for HAE, except Berinert P®, was licensed in Japan at the time of this survey,
time from the onset of attack to the injection of pdC1-INH is a rate-limiting factor that affects the duration of the attack. Time of travel from the onset of symptoms to the arrival at hospital was $31.9 \pm 18.4$ min (mean $\pm$ SD, median 33.8, $n = 40$). In addition, an even longer duration of time was required from the time of arrival ($55.1 \pm 41.2$ min, median 45.0, $n = 40$) to finally receiving an injection of pdC1-INH at appropriate unit in the hospital. Thus, $87.0 \pm 44.3$ min (median 90.0, $n = 40$) was required in total for the commencement of proper treatment (Fig. 5a,b).

Moreover, only 5 out of 43 (11.6%) patients reported that their

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**Fig. 2.** Analysis of attacks during recent past 1 year. (a) The number of attacks of 61 patients are shown. The histogram shows the distribution of patients in the order of frequency of attacks each had in the past one-year period (horizontal axis), with color-coding the frequencies of treated vs. untreated attacks. Bars in red indicate attacks without treatment, and bars in blue indicate treated ones. The horizontal dotted line indicates an average (A data reporting 350 time/year was removed from analysis, because it seems to be clearly incorrect). (b) The frequency of attacks ($n = 69$) is divided to following groups; high frequency: more than 20 times/year, low frequency: 1–19 times/year, No. attacks in the last year, Never had attack. (c) The ratio of receiving treatment or not was calculated from 960 attacks of 61 patients.

**Fig. 3.** Days of hospitalized and absent from work/school in a year. (a) Days of hospitalization due to attack ($n = 46$). Three outliers are present in the before diagnosis section. (b) Days absent from work/school due to attack ($n = 38$). Means $\pm$ SEMs are indicated as blue lines. Statistical significance between before and after diagnosis is calculated by Wilcoxon matched-pairs signed rank test.
symptoms of HAE completely disappeared within 5 h, and symptoms of 29 patients (67.4%) lasted for a day or longer (Fig. 6b). However, there was no significant correlation between required time from attack to injection and patient reported effectiveness of treatment (data not shown). With regard to signing of a consent form before receiving injection of pdC1-INH, 23 out of 46 patients (50.0%) reported having to sign every time (Supplementary Fig. 5).

For prophylaxis, 42 out of 70 (60.0%) patients regularly take medication for long-term prophylaxis, while others 8 (11.4%) took medication only when they feel an attack is likely and 13 (18.6%) patients took no prophylactic medication, regardless of the symptoms (Fig. 7a). There was no difference in the use of prophylactic treatments between the high frequency and low frequency groups (data not shown). Among the commonly used medications for HAE, oral tranexamic acid was used by most patients (77.6%, n = 38/49), followed by danazol (20.4%, n = 10/49) and C1-INH concentrate (2.0%, n = 1/49) (Fig. 7b). However, only small number of the patients reported that the prophylactic treatment they are using was “very effective” (7.1%) or “effective” (21.4%), in comparison with the treatment for acute attacks (Fig. 7c). The 39.7% (n = 27/68) of patients carried emergency card of HAE. The patient journey found in this study was graphically summarized in Figure 8.

Variable cluster analysis

We investigated the relevance of 13 questions out of a total of 48 questions in this study. Forty-one variables were considered for classification into 8 clusters (Supplementary Fig. 6). Following relationships were found:

1) A diagnosis of HAE in a dermatology department is related to the prescription of steroids (cluster No.3)
2) Satisfaction with treatment is related to regular visits and the time required to travel to the hospital in an emergency (cluster No.5)
3) The following symptoms form a cluster, so patients who report experience of one tend to also report experience of at least one other in this group: dyspnea, malaise, shortness of breath, breathing difficulty, skin rash (cluster No.6)
4) Stomach ache, nausea, and diarrhea also tend to occur together, and those patients reporting experience of these symptoms indicated that they had experienced these symptoms together since the onset of attacks (cluster No.7).
5) Vertigo and hypotension tend to occur concurrently, and those reporting symptoms up to now tend to have experienced such symptoms from the onset of HAE attacks (cluster No.8)

Discussion

HAE is a rare and life-threatening hereditary disease. Severity of the disease is largely variable not only among patients, but also over the life course of individual patients. The picture of symptoms reported in this patient reported survey are generally of a more severe nature, in terms of frequency and impact of attacks compared to that reported in the Ohsawa et al., 2015 study based on a questionnaire to physicians. The average numbers of attacks (15.7 times), days hospitalized (4.2 days) and absent from work or school (10.2 days) in a year were higher, at 6.2 attacks, 1.8 days and 1.7 days respectively, than in the survey conducted by Ohsawa et al. The results reported here are comparable with those in patient reported outcome surveys overseas. A patient reported outcome
Fig. 5. Time from attacks to receiving injection. (a) Time required from onset of attack to arriving hospital (blue) and that until receiving injection of pdC1-INH (red) (n = 40). The horizontal dotted line indicates the average. (b) The average and standard deviation of the time to arriving at hospital and that to receiving pdC1-INH.

Fig. 6. Clinical effect of pdC1-INH injection for acute attack. (a) Average of duration from pdC1-INH injection to the time when symptoms started to disappear (n = 41). (b) Average of duration from pdC1-INH injection to the complete disappearance of the symptoms (n = 43).
A survey conducted at a HAE patient summit in the United States showed that 25% of patients were experiencing one or more attacks per week and 48% of patients had one or more attacks per month, which are outcomes similar to the results in this survey. A European patient oriented study about days lost from work/school as a result of HAE attacks found an average of 19.9 days (median 8.0 days) were missed per year, which is even larger than that in our survey. Delay in diagnosis for HAE is a problem in many countries. The delay in diagnosis reported in the scientific literature is 16 years in Denmark, 13 years in Spain, 10 years in the United Kingdom, and 8 years in the United States. Closer to home, a survey from Asia reported that it took 7.8 ± 10.5 years in South Korea for a definitive diagnosis. Taken together, this data shows that delayed diagnosis is an issue for HAE patients all over the world, but the delay is particularly long in Japan (15.6 ± 13.3 years).

Generally, due to raised awareness about HAE, among other things, the time from first symptoms to diagnosis is shortening. Recently a registry system in Europe showed that average delay in diagnosis was 9 years. Internationally, the period until diagnosis of patients in the younger generation, born during the period 1980–1990, has reduced to 1.4 years from 7.0 years compared to patients born during 1950–1960. In this study, the average period from initial symptom to diagnosis was 23.3 ± 15.6 years in the patients born before 1960, which was shorter to 9.0 ± 8.3 years in younger generation (birth after 1980).

Disease awareness is an important factor for the diagnosis of HAE. It is unlikely that physicians with no awareness of HAE can make a proper diagnosis. Given this situation, a survey of 9279 medical doctors in Japan (4495 respondents, 48.4% response rate) showed that only 44.8% had even a basic degree of awareness about HAE. This low awareness may explain, in part, why, the rate of diagnosis at the first medical institutions visited in our survey was as low as 12%, and an average of 4.6 different specialty departments were required to diagnosis of HAE. Eighty percent of patients experienced abdominal symptoms as well as visible skin symptoms, and most patients visited general medicine, gastroenterology, and/or dermatology departments before being diagnosed. Patients presenting with abdominal symptoms, were often misdiagnosed as having gastrointestinal disease or appendicitis, and with skin swelling an allergy reaction was a frequent diagnosis. We can assume this is due to low disease awareness of HAE and its various symptoms. Consequently, gastrointestinal drugs, antiallergic drugs, corticosteroids, antibacterial drugs, painkillers, etc. were prescribed in many cases.

The genetic test of C1–INH gene could directly provide definitive diagnosis, but measuring C1–INH activity and complement C4 may be sufficient in many cases for diagnosis with HAE. Genetic testing was carried out in the case of 20.8% patients in Japan, and 26.9% of all relatives of the affected families. The reason for the low implementation rate of genetic testing may be because it was not essential for diagnosis of HAE and due to a limited number of facilities where genetic testing is possible. This study included 7 diagnosed cases of asymptomatic patients. The number of days absent from work or hospitalized due to attacks significantly decreased after being diagnosed with HAE. Early diagnosis of HAE, ideally before the onset of HAE, would help with preventive care in advance of the onset of symptoms and with prompt treatment at the time of attack. For this purpose, steps need to be taken to include the disease awareness of medical doctors as well as promoting screening or genetic testing for relatives of HAE patients. It is also important to raise the awareness of patients and public through social media, such as HAE-related websites.

This patient reported outcomes survey found that there was a large variation in number of attacks among patients from 0 to 100 times/year. The percentage of treated attacks remained at 53%, and the rate of treatment varied from patient to patient regardless of the frequency of attacks. Each patient may decide whether or not to seek treatment depending on the severity of the attack. This survey
was conducted at a time when a home self-treatment was not available to patients in Japan. It is expected that the percentage of attacks treated will increase now that a home therapy has been approved. Home therapy by self-injection has been introduced in many countries and 91% of patients are treating themselves at home.9

In our survey, pdC1-INH was the most commonly used (82.3%) acute attack therapy followed by tranexamic acid (tablet and injection). Approximately 70% of patients reported that the acute attack treatment being used was effective. While high, it also suggests that for some patients receiving pdC1-INH the treatment was not seen as effective. pdC1-INH should be administered promptly when an attack occurs, but it takes an average of 87 min from patient recognition that they are having an attack until receiving treatment by injection. The waiting time required for the injection at hospital (about 55 min) was longer than that of travel time from home to the hospital (about 32 min). This waiting time may reduce the efficacy of the treatment. It has been reported that early administration of pdC1-INH shortens the duration and severity of the attack.11 In this survey, only 14.6% of patients reported relief of symptoms within 30 min, and only 11.6% of patients experienced complete relief of symptoms within 5 h. From this result, its expected that improvements will be achieved with the introduction of home treatment (ex. Icatibant).

In Japan, generally only large university hospitals or regional hospital hubs treat rare disease patients and HAE patients need to go to these centers to receive pdC1-INH to treat attack. Possible reasons for the long wait time are that these hospitals are generally crowded during normal working hours and it is not always possible to be seen immediately. Out of hours, there are only a few hospital staff working, and the doctor on duty may be unfamiliar with handling pdC1-INH. There may not be a nurse available to prepare the medication. As special pharmaceutical product, it can also take time to request and receive the product. In addition, 45% of patients had to sign a letter of consent before receiving pdC1-INH at every treatment, which may also add to the wait time.

Sixty percent of patients reported receiving medications for long-term prophylaxis. However, most were using tranexamic acid, and only 28.5% of the patients thought the prophylaxis treatments were effective. In addition, 18.6% of patients reported receiving no prophylactic treatment options. International guidelines for HAE do not recommend tranexamic acid as a medication for long-term prophylaxis.1 A systematic review of tranexamic acid reported some positive effects of this medication compared with no treatment, but there is only limited evidence of prophylaxis efficacy.13 In a European study, it was found that 34% of patients were receiving long-term prophylaxis and approximately 70% were using androgens.15 Nevertheless, androgen therapy is not authorized for HAE in Japan and its efficacy is not as high as modern therapies. pdC1-INH has been used successfully as a long-term prophylactic in many parts of the world. In addition, new preventive treatments using biologics are now available in the US and parts of Europe and these are breakthrough therapies with extremely high levels of efficacy.20

It is recommended that patients with HAE should always carry emergency ID card of HAE to receive treatment smoothly even at other medical institutions during attack. However, the ownership rate is still 40%. It is necessary to intensify activities to raise awareness for HAE and to increase emergency card carrying. We also need to work with hospitals so that they are willing to treat HAE patients from other hospitals if there are in the locale and in need of treatment.

The limitation of this study is the small number of patients with potential bias in recruitment. In fact, the frequency of attacks in this survey was higher than those reported by Ohsawa et al., suggesting the possibility that patients answering to this survey may suffer from severer symptoms than those previously reported by physicians in Japan. On the other hand, physician-reported surveys may underestimate attacks as it is possible that patients do not
retrospectively report all HAE incidents during a routine hospital appointment. In fact, 46.9% of attacks in this survey were not treated and therefore may have gone unrecorded by their physician.

Despite these limitations, the patient reported outcome survey may reveal more accurately the pathway to diagnosis, the frequency and severity of attacks and the pattern of treatment than a physician reported survey. The attack locations in the body in this study were similar to, but attacks more frequent, than previously reported in Japan based on the information collected via physicians. Notably, the severity and characteristics of HAE attacks revealed in this survey are similar to those in international patients reported in Japan based on the information collected via physicians.

Acknowledgments

This work was supported by a research grant from the Shire (now in a part of Takeda) Japan.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2020.09.008

Conflict of interest

IO has received honoraria as a speaker/advisor from BioCryst, CSL Behring, and Shire. TH has received honoraria as a speaker from Takeda and CSL Behring. AF has received fees for speaking from Shire and CSL Behring.

MH has received honoraria as a speaker/advisor from BioCryst, CSL Behring, and Shire. He has also received institutional research funding from CSL Behring. The rest of the authors have no conflict of interest.

Authors’ contributions

KI, BY, IO and MH designed the study and wrote the manuscript. KI and MH performed the statistical analysis. TA designed and performed variable cluster analysis. All authors performed interpretation of the results and approved the final manuscript.

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