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Physician awareness and understanding of hereditary angioedema: A web-based study in Japan

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Abstract

Objectives: Hereditary angioedema (HAE) is a rare disease with acute attacks in the skin and mucosa throughout the body including life-threatening laryngeal edema and abdominal attacks with severe pain. Physicians, regardless of specialty, may encounter HAE patients in their daily practice; however, low disease awareness may attribute to a considerable number of undiagnosed HAE patients in Japan. This study aims to identify issues associated with the diagnosis processes of HAE and to determine levels of HAE awareness among Japanese physicians from various specialties.

Methods: A web-based quantitative survey was conducted using a physicians panel. Physicians from the following departments were included in the survey: internal medicine, dermatology, pediatrics, emergency medicine, and gastroenterological surgery.

Results: The proportions of physicians in dermatology, pediatrics, emergency medicine, internal medicine, and gastroenterological surgery who were able to select the C1-INH activity test as a diagnosis test for potential HAE patients were 71.8%, 59.7%, 57.1%, 40.3%, and 25.7%, respectively. Multivariate analysis showed significant association between physicians who selected "strongly suspected" AE based on the case-scenario and physicians who had knowledge of the essential HAE symptoms (laryngeal edema, swelling after tooth extraction, swelling of the tongue, and abdominal pain).

Conclusions: This study showed that disease awareness of HAE varied among medical specialties, suggesting the importance of educational activities in academic societies and specialist accreditation in raising HAE awareness. Proper knowledge of complement testing and HAE symptoms may help not only to diagnose patients with AE-like symptoms as AE but also to differentially diagnose HAE from AE.

KEYWORDS
abdominal pain, airway obstruction, angioedema, Angioedemas, hereditary, surveys and questionnaires

1 | INTRODUCTION

Hereditary angioedema (HAE) is a rare disease characterized by recurrent attacks of unpredictable edema occurring anywhere in the body. Laryngeal attacks are especially life threatening, while abdominal attacks are sometimes erroneously treated with laparotomy. The global prevalence of HAE is estimated to be one in 10,000[1] to one in 50,000.[2] It is estimated that there are about 2500 patients with HAE in Japan,[3] but only 450 patients have been reported there as of 2018,[4] suggesting that there may be many patients with undiagnosed HAE. The average time between symptom onset and diagnosis is approximately 8 years in the United States and 10 years in the United Kingdom, while it is approximately 16 years in Japan, which is a significantly longer time to proper HAE diagnosis than in other countries.[5–7] HAE is mostly associated with a deficiency in the functional C1 inhibitor (C1-INH) and is classified into three types based on the causes of the defect: Types I and II are caused by low levels and normal levels but disfunction of C1-INH individually. Type III or HAE with normal C1INH is very rare.

The problem with the diagnosis of HAE in Japan is considered to be attributable to the low level of awareness among Japanese physicians.[8] In a survey of 4495 physicians from all medical departments in 2008, there were only 2015 physicians (44.8%) who had knowledge about HAE, including 1038 physicians who had actually saw HAE patients.[8] In addition, of the 2480 physicians who did not know about HAE, 285 reported that they had seen suspected HAE patients, including 641 missed cases.[8] The results of this survey suggested that HAE may not be detected easily in patients in Japanese outpatient clinics.

Symptoms suggestive of angioedema (AE) include subcutaneous edema, submucosal edema, gastrointestinal (GI) symptoms (abdominal pain, nausea, vomiting and diarrhea), laryngeal edema, and convulsions.[3] Patients with dyspnea and abdominal pain as the main symptoms are likely to consult with general physicians or internal medicine doctors from any specialty. Other experts that HAE patients may initially consult with include ER physicians, gastroenterological surgeons, dermatologists, rheumatologists, and nephrologists who have experience with edema symptoms.

There is one report in which the degree of awareness and understanding of HAE by physicians in Japan at hospitals with more than 100 beds were investigated,[8] but the diagnostic process by specialty was not evaluated in the study. In addition, the degree of recognition of the diagnosis and treatment of HAE for each type of clinical department has not been confirmed. Therefore, this study aimed to clarify the awareness of HAE and differential diagnosis among Japanese physicians from different specialties and all types of medical facilities including hospital and clinics. In addition, we clarified the flow of diagnosis in Type I and II HAE and the level of understanding of the factors for investigating the disease in clinical practice in Japan.

2 | METHODS

2.1 | Study design

The study employed a noninterventional, cross-sectional design to collect data via a web-based quantitative survey through a commercially available physician panel. The subjects were 692 physicians who were recruited through the Nikkei BP Panel (NBP) and were required to meet the inclusion and exclusion criteria for participation in the research. The study protocol was approved by the Non-Profit Organization MINS Institutional Review Board (Approval No. MINS-IRB 200244). Informed consent was obtained from all participating physicians. The target physicians were members of Nikkei Medical Online, a portal site run by Nikkei BP (Tokyo, Japan) that provides medical information for physicians and medical professionals. As of October 31, 2017, it had 153,666 members.[9] The total target number of physicians for this survey was 600 or more, with 200 or more from internal medicine, and 100 or more each from dermatology, pediatrics, emergency medicine, and gastroenterological surgery. The sample sizes for each diagnostic and treatment department were chosen to roughly reflect the number of physicians treating HAE patients in their respective departments. As internal medicine includes doctors from multiple specialties, the number of physicians from internal medicine was made twice the number of the specialty departments. The total sample size was set at a minimum of 600 physicians due to time and resource constraints when recruiting physicians and conducting the survey.

2.2 | Selection of research subjects

Physicians who are member of Nikkei Medical Online were invited to participate and their eligibility was reviewed. The questionnaire for physicians consisted of three screening items and 14 survey items (Table S1).

Physicians specializing in internal medicine (general medicine, cardiology, gastroenterology, pulmonary medicine, nephrology, hematology, geriatrics, endocrinology, diabetes, infectious diseases, neurology, or rheumatology), dermatology, pediatrics, emergency medicine, and gastroenterological surgery were targeted for this study. Physicians who had less than 1 year of practice after their training period, who mainly worked in facilities other than clinics, university hospitals, general hospitals or national/public hospitals, or who did not belong to any medical society were excluded.

2.3 | Surveillance procedures

The questions consisted of two large sections based on the case presentation (questions 1 to 8; Table S1) and the physician's actual experience in everyday medical practice (questions 9 to 11; Table S1),

as well as other sections that asked about participant demographics and characteristics. Questions 1 to 6 were designed to provide a fictitious case of suspected HAE patient with difficulty of breathing (Table 1) to clarify the level of physician awareness of HAE and its diagnosis, including the disease to be suspected, the order in which the diseases should be suspected, the tests that were most helpful in diagnosis, the required complementary tests, the most important medical histories to ask patients, and the methods of follow-up. The fictious case of suspected HAE patient is intended to be the one with either Type I or II HAE. Questions 7 and 8 (Table S1) presented the four symptoms of HAE (subcutaneous edema, submucosal edema, digestive symptoms, and medical history or symptoms of edema of larynx) and dummy symptoms of anaphylaxis, and the five diseases (food-dependent and exercise-induced anaphylaxis, HAE, idiopathic angioedema, oral allergy syndrome and eosinophilic gastroenteritis), and physicians were asked about their level of suspicion for each disease and the most suspicious disease for each symptom. The results were used to assess the relationship between knowledge of the complement system and accurate diagnosis of HAE (Q3; Table S1), knowledge about the most important serum markers, C4 and C1 esterase inhibitor (C1-INH), for HAE diagnosis (Q4; Table S1), the thought stream of physicians during consultation (Q5; Table S1), and treatment and follow-up of suspected HAE patients and misdiagnosed HAE patients (Q6; Table S1). In Q4 to measure knowledge of the most important complementary tests, being able to choose C1-INH activity is at least necessary for HAE diagnosis. Further details about the questions and answer options, as well as the presented case-report, are listed in Tables 1 and S1.

TABLE 1 Case-scenario and keywords

Case-scenario
Gender/Age: Female, 26 years old Chief complaint: Difficulty of breathing Medical history: Hospitalized for laryngeal and pharyngeal edema at 15, 17 and 18 years of age; hospitalized for acute abdomen at 23 years of age. A large amount of ascites was noted, but it resolved spontaneously after 2 days. In her teenage years, edema of the extremities and face appeared about once a month which spontaneously disappeared in a few days. On admission: There were no abnormal findings in the oral cavity or face, but edema was noted in the neck and dorsal left leg. Blood pressure, pulse rate, and temperature were within normal ranges. Blood tests showed no evidence of inflammation and no electrolyte abnormalities. A cervical CT showed an edema under the skin of the anterior neck. The edema was not found on the throat and the pharynx. There was no airway stenosis. **Disease set:1.** Heart failure **2.** Cachexia caused by malignancy **3.** Immediate allergic attacks caused by allergens such as food **4.** Angioedema **5.** Systemic inflammation due to collagen diseases
Keywords
Subcutaneous edema (e.g., extremities and face) Submucosal edema (intraoral, gastrointestinal and vulvar) Gastrointestinal symptoms (abdominal pain, nausea, vomiting and diarrhea) Patients with a history of laryngeal edema and symptoms **Disease set:1.** Food-dependent and exercise-induced anaphylaxis **2.** Hereditary angioedema **3.** Idiopathic angioedema **4.** Oral allergy syndrome **5.** Eosinophilic gastroenteritis

Abbreviation: CT, Computed tomography.

2.4 | Statistical analyses

After informed consent was obtained, all physicians included in the survey were screened for eligibility criteria. Descriptive analyses were performed to assess the quantitative nature of the data collected and the characteristics of the samples investigated. All categorical variables were analyzed using frequency tables (absolute and relative frequencies), and all continuous variables were analyzed using summary statistics (mean, standard deviation, minimum, maximum, median, and quartiles). In order to evaluate the relationship between the diagnosis of HAE and knowledge of HAE symptoms, all answer options measuring "knowledge of symptoms" (Q11; Table S1) of HAE were analyzed using a multiple logistic regression model to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CI). The same analyses were performed for the answer options of "strongly suspect" for AE (Q1: Case-scenario question; Table S1) and HAE (Q7: Keyword question; Table S1). The adjusted ORs describe the relationships between particular explanatory variables and the choice of "high suspicion" while simultaneously controlling for all other variables. All analyses were performed using R version 4.0.2 statistical software.

3 | RESULTS

3.1 | Physician demographics

Figure 1 shows the flow of the study design and the process for selecting participants. Of 1170 physicians who accessed the questionnaire site, the 692 physicians (response rate: 59.1%) who responded to the questionnaire during the survey period were included. Overall, 151 physicians met the exclusion criteria and 307 physicians did not complete the entire questionnaire.

Table 2 summarizes the baseline demographics of the study participants. The distribution of participating physicians by medical department was as follows: 238 from internal medicine, 110 from dermatology, 119 from pediatrics, 112 from emergency departments, and 113 from gastroenterological surgery. The majority (88.9%) of the 615 physicians were male and 77 (11.1%) were female. The overall mean age was 48.6 years (standard deviation = 10.9). Approximately one-third of the participants worked primarily at general hospitals (35.7%), followed by clinics, national/public hospitals (23.0% each), and university hospitals (18.4%).

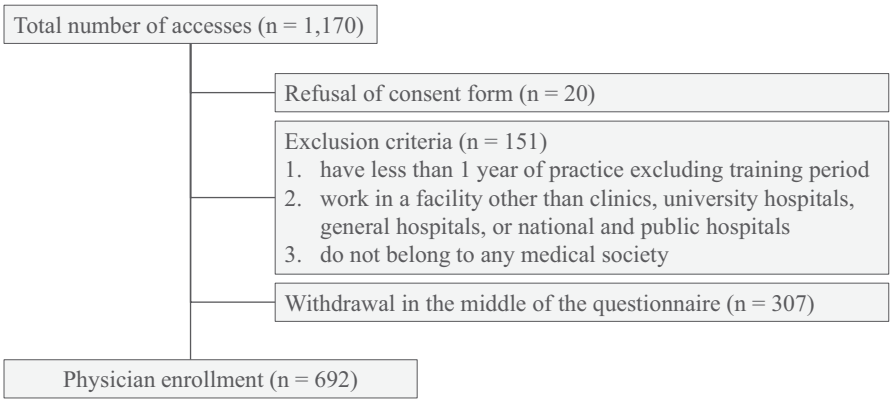

FIGURE 1 Study identification and selection process

Figure 2 shows the proportions by disease suspected by physicians as the first choice in the Q2 (Case-scenario; Table 1 and questions; Table S1; Figure 2A) and the Q8 (Keyword question; Table S1; Figure 2B). In the case of scenario Q2, the physicians who selected "angioedema" as the correct answer as their first choice comprised 67.3% of all physicians, 61.8% of internal medicine physicians, 72.7% of dermatologists, 83.2% of pediatricians, 73.2% of emergency physicians, and 51.3% of gastroenterological surgeons. Incorrect answers for all physicians were heart failure (1.9%), cachexia associated with malignant tumor (0.3%), immediate-type allergic attack due to food or other allergens (15.2%), and systemic inflammation due to collagen disease (7.8%). For the Q8 keyword question, the physicians who selected "HAE" as the correct answer as their first choice comprised 40.9% of all physicians, 39.9% of internal medicine physicians, 43.6% of dermatologists, 52.1% of pediatricians, 42.9% of emergency physicians, and 26.5% of gastroenterological surgeons. Idiopathic angioedema was selected by 27.2% of all physicians, 24.8% of internal medicine physicians, 34.5% of dermatologists, 28.6% of pediatrics physicians, 21.4% of emergency physicians, and 29.2% of gastroenterological surgeons. The percentage of incorrect answered selected by all physicians were food dependent and exercise-induced anaphylaxis (19.5%), idiopathic angioedema (27.2%), oral allergy syndrome (5.1%), and eosinophilic gastroenteritis (6.9%).

The results stratified by years since graduation from medical school were shown in Table S2. There was no clear relationship between AE knowledge and years since graduation. The proportions of physicians who correctly chose "strongly suspect" AEs in the case-scenario question (Q1; Table S1) comprised 53.8% among physicians within 4 to 9 years after graduation and 49.8% among physicians 10 years or more since graduation. The OR of the selection of the "strongly suspect" answer option of AE in case scenario (Q1; Table S1) was 1.17 (95% CI 0.73-1.87) between the two groups. The proportions of physicians who "strongly suspected" HAE based on the keywords (Q7; Table S1) comprised 32.5% for physicians within 4 to 9 years since graduation and 38.9% for physicians 10 years or more since graduation. The OR of the selection of the "strongly suspect" answer option was 0.76 (95% CI 0.46-1.24) between the two groups.

Table 3 shows the question options for the various HAE case-scenarios. In the Q3 (Table S1) case-scenario, the proportions of physicians who selected "complement system" as the appropriate lab test comprised 63.2% of all physicians, 54.2% of internal medicine physicians, 80.0% of dermatologists, 69.7% of pediatricians, 73.2% of emergency physicians, and 48.7% of gastroenterological surgeons. The proportions of physicians who answered that "family history" should be checked as the most important item in the interview in Q5 (Table S1) comprised 51.0% of all physicians, 43.3% of internal medicine physicians, 66.4% of dermatologists, 60.5% of pediatricians, 56.3% of emergency physicians, and 37.2% of gastroenterological surgeons. Other answers among all participants were "allergy history" (22.4%) and "disease history" (17.5%).

Q6 (Table S1) was used to measure how patients were treated and followed up in the case-scenario. The proportions of physicians who answered "to hospitalize" the patients in the case-scenario comprised 65.9% of all physicians, 63.0% of internal medicine physicians, 64.6% of dermatologists, 71.4% of pediatricians, 68.7% of emergency physicians, and 64.6% of gastroenterological surgeons.

As shown in Table 3, the proportions of physicians who were able to choose complement system in Q3 (Table S1) and answer "C1-INH activity" in question Q4 (Table S1) regarding complement system markers comprised 49.0% of all physicians, 40.3% of internal medicine physicians, 71.8% of dermatologists, 59.7% of pediatricians, 57.1% of emergency physicians and 25.7% of gastroenterological surgeons. The proportions of physicians who chose complement system in Q3 (Table S1) and answered "C1-INH activity and C4" in the question comprised 18.9% of all physicians, 12.6% of internal medicine physicians, 34.5% of dermatologists, 22.7% of pediatricians, 21.4% of emergency physicians, and 10.6% of gastroenterological surgeons. Table S4 shows the proportion of physicians who were able to choose "complement system" for question Q3 (Table S1) and their answers for question Q4 (Table S1) by region. The proportion of physicians who selected an answer including C1-INH was higher in the Hokkaido (88.9%), Kanto (68.6%), Kinki (70.4%) areas and lower in the Tohoku (57.1%), Chubu (67.3%), Chugoku (67.3%), Shikoku (65.0%), and Kyushu and Okinawa (58.8%) areas than the result in total (67.9%). The proportion of physicians in each region who selected "C1-INH activity and other complement system" for question Q4 were as follows: 61.1% in the Hokkaido area, 48.6% in the Tohoku area, 50.2% in the Kanto area, 47.3% in the Chubu area, 50.0% in the

TABLE 2 Demographic characteristics of the participants

	No. (%) respondents					
	Total	Internal medicine	Dermatology	Pediatrics	Emergency medicine	Gastroenterological surgery
	n = 692	*n* = 238	*n* = 110	*n* = 119	*n* = 112	*n* = 113
Sex						
Male	615 (88.9)	220 (92.4)	83 (75.5)	102 (85.7)	102 (91.1)	108 (95.6)
Female	77 (11.1)	18 (7.6)	27 (24.5)	17 (14.3)	10 (8.9)	5 (4.4)
Age						
Mean	48.6	49.8	48.4	48.7	44.6	50.0
SD	10.9	11.1	11.2	11.5	9.5	10.2
Years of experience						
4-9 years	80 (11.6)	25 (10.5)	12 (10.9)	15 (12.6)	17 (15.2)	11 (9.7)
10-19 years	202 (29.2)	65 (27.3)	27 (24.5)	36 (30.3)	48 (42.9)	26 (23.0)
20-29 years	208 (30.1)	72 (30.3)	38 (34.5)	29 (24.4)	28 (25.0)	41 (36.3)
30-39 years	178 (25.7)	71 (29.8)	28 (25.5)	33 (27.7)	18 (16.1)	28 (24.8)
More 40 years	24 (3.5)	5 (2.1)	5 (4.5)	6 (5.0)	1 (0.9)	7 (6.2)
Region						
Hokkaido	36 (5.2)	10 (4.2)	8 (7.3)	5 (4.2)	6 (5.4)	7 (6.2)
Tohoku	35 (5.1)	12 (5.0)	5 (4.5)	7 (5.9)	5 (4.5)	6 (5.3)
Kanto	207 (29.9)	71 (29.8)	42 (38.2)	42 (35.3)	31 (27.7)	21 (18.6)
Chubu	110 (15.9)	41 (17.2)	19 (17.3)	17 (14.3)	21 (18.8)	12 (10.6)
Kinki	152 (22.0)	43 (18.1)	20 (18.2)	30 (25.2)	25 (22.3)	34 (30.1)
Chugoku	52 (7.5)	22 (9.2)	4 (3.6)	5 (4.2)	6 (5.4)	15 (13.3)
Shikoku	20 (2.9)	12 (5.0)	4 (3.6)	1 (0.8)	2 (1.8)	1 (0.9)
Kyushu Okinawa	80 (11.6)	27 (11.3)	8 (7.3)	12 (10.1)	16 (14.3)	17 (15.0)
Hospital type						
Clinic	159 (23.0)	67 (28.2)	48 (43.6)	36 (30.3)	5 (4.5)	3 (2.7)
University hospital	127 (18.4)	33 (13.9)	19 (17.3)	19 (16.0)	31 (27.7)	25 (22.1)
National and public hospitals	159 (23.0)	42 (17.6)	21 (19.1)	26 (21.8)	38 (33.9)	32 (28.3)
General hospital	247 (35.7)	96 (40.3)	22 (20.0)	38 (31.9)	38 (33.9)	53 (46.9)
Professional memberships						
The Japanese Society of Internal Medicine	247 (35.7)	215 (90.3)	2 (1.8)	2 (1.7)	27 (24.1)	1 (0.9)
Japan Pediatric Society	129 (18.6)	3 (1.3)	1 (0.9)	119 (100)	6 (5.4)	0 (0.0)
The Japanese Society of Gastroenterology	119 (17.2)	56 (23.5)	0 (0.0)	0 (0.0)	4 (3.6)	59 (52.2)
The Japanese Circulation Society	59 (8.5)	52 (21.8)	0 (0.0)	2 (1.7)	5 (4.5)	0 (0.0)
The Japanese Respiratory Society	38 (5.5)	36 (15.1)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Japanese Society of Nephrology	27 (3.9)	24 (10.1)	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)
The Japan Diabetes Society	41 (5.9)	36 (15.1)	0 (0.0)	5 (4.2)	0 (0.0)	0 (0.0)
Japanese Association for Acute Medicine	135 (19.5)	10 (4.2)	0 (0.0)	3 (2.5)	109 (97.3)	13 (11.5)

TABLE 2 (Continued)

	No. (%) respondents					
	Total	Internal medicine	Dermatology	Pediatrics	Emergency medicine	Gastroenterological surgery
	n = 692	*n* = 238	*n* = 110	*n* = 119	*n* = 112	*n* = 113
The Japan Endocrine Society	18 (2.6)	12 (5.0)	0 (0.0)	5 (4.2)	0 (0.0)	1 (0.9)
The Japanese Association for Infectious Diseases	42 (6.1)	19 (8.0)	1 (0.9)	8 (6.7)	10 (8.9)	4 (3.5)
Japan College of Rheumatology	18 (2.6)	12 (5.0)	4 (3.6)	2 (1.7)	0 (0.0)	0 (0.0)
Japanese Society of Allergology	62 (9.0)	14 (5.9)	20 (18.2)	27 (22.7)	1 (0.9)	0 (0.0)
The Japan Geriatrics Society	22 (3.2)	22 (9.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Japanese Society of Neurology	41 (5.9)	41 (17.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
The Japanese Society of Hematology	15 (2.2)	9 (3.8)	0 (0.0)	5 (4.2)	1 (0.9)	0 (0.0)
The Japanese Society of Gastroenterological Surgery	122 (17.6)	5 (2.1)	0 (0.0)	0 (0.0)	5 (4.5)	112 (99.1)
The Japanese Dermatological Association	113 (16.3)	2 (0.8)	109 (99.1)	0 (0.0)	2 (1.8)	0 (0.0)

Kinki, Chugoku, and Shikoku areas, and 40.0% in the Kyushu and Okinawa area. The proportions of physicians in each region who selected "C4 and C1-INH activity" for question Q4 were as follows: 27.8% in the Hokkaido area, 8.6% in the Tohoku area, 18.4% in the Kanto area, 20.0% in the Chubu area, 20.4% in the Kinki area, 17.3% in the Chugoku area, 15.0% in the Shikoku area, and 18.8% in the Kyushu and Okinawa area.

Answers for questions regarding the HAE diagnosis experience, signs and symptoms (Q9 and Q10; Table S1) are summarized in Table 4. The proportions of physicians who had actual experience of HAE cases, including suspected cases, comprised 53.9% of all physicians, 50.0% of internal medicine physicians, 80.0% of dermatologists, 52.1% of pediatricians, 68.7% of emergency physicians, and 23.0% of gastroenterological surgeons. The proportions of physicians who have actually seen suspected HAE patients but diagnosed them otherwise comprised 38.1% of all physicians, 28.6% of internal medicine physicians, 45.5% of dermatologists, 50.8% of pediatricians, 31.2% of emergency physicians, and 46.2% of gastroenterological surgeons.

The appropriate answers for the symptoms of HAE (Q11; Table S1) in Table 4 were subcutaneous edema (78.6%), laryngeal edema (80.5%), abdominal pain (61.6%), swelling after tooth extraction (20.1%), and swelling of the tongue (54.9%). While 91.9% of physicians selected some of the appropriate answers, the percentage of physicians who selected all the correct answers but with some incorrect ones, decreased to 13.2%. Only 2.9% of physicians selected all and only the five correct answer options that are listed in Table 4.

Figure 3 shows the relationship between the physicians who selected "strongly suspect" for AE (Q1; Table S1)/HAE (Q7; Table S1) and knowledge of HAE symptoms (Q11; Table S1: subcutaneous edema, laryngeal edema, abdominal pain, swelling after tooth extraction, and swelling of the tongue); the ORs are shown in Table S3. Multivariate analysis showed that there were four variables significantly related to the selection of "strongly suspect" AE in the case scenario question: laryngeal edema (OR = 1.80; 95% CI 1.07-3.07), abdominal pain (OR = 1.94; 95% CI 1.34-2.82), tongue swelling (OR = 1.81; 95% CI 1.28-2.57), and swelling after tooth extraction (OR = 2.09; 95% CI 1.31-3.33). Similarly, multivariate analysis in Q7 (Keyword question) showed that there were two symptoms significantly related to the selection of "strongly suspect" HAE: laryngeal edema (OR = 3.19; 95% CI 1.72-5.90) and swelling after tooth extraction (OR = 2.14; 95% CI 1.38-3.33).

4 | DISCUSSION

This study evaluated the awareness of HAE among physicians in Japan and the process of diagnosis by their specialty. Figure 4 summarizes the physicians' thinking process when consulting a suspected HAE patient based on the case scenario. Overall, 692 physicians from all types of responded via the NBP website. This is the first attempt in Japan in

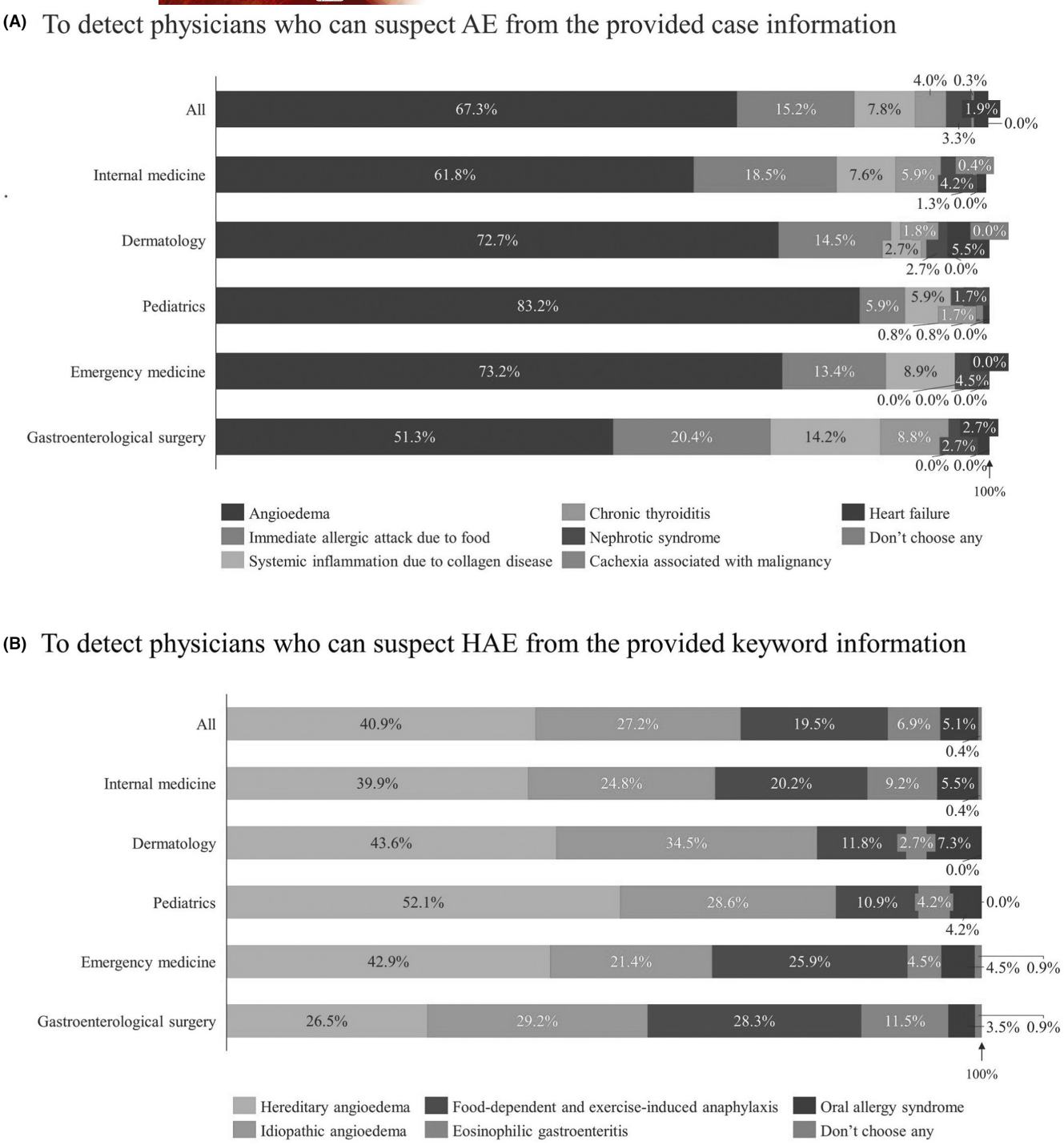

FIGURE 2 First suspected disease. (A) First suspected disease based on the presented case-scenarios (Q2; Table S1). (B) First suspected disease based on the presented symptoms (Q8; Table S1). AE, Angioedema; HAE, Hereditary Angioedema

using a web-based questionnaire in Japan to evaluate HAE knowledge and factors affecting diagnosis among physicians from various specialties, and awareness of HAE in different clinical departments from all types of medical facilities including hospital and clinics. It also revealed the flow of diagnosis of HAE and the level of understanding of the factors that affect the diagnosis in different clinical settings.

Awareness of HAE varied among medical specialties. In particular, internal medicine physicians and gastroenterological surgeons tended to have lower awareness of HAE than physicians in other medical specialties. Dermatologists were more aware of HAE because their specialty is the one most associated with edema symptoms. Awareness of HAE in emergency departments and pediatrics was also relatively high. Regarding the association between the post-graduation years and the knowledge of HAE and AE, there were no significant differences between the two stratified groups. Disease awareness among pediatricians and

TABLE 3 Knowledge of examination, and follow-up for diagnosis of AE

	No. (%) respondents					
	Total	Internal medicine	Dermatology	Pediatrics	Emergency medicine	Gastroenterological surgery
	n = 692	*n* = 238	*n* = 110	*n* = 119	*n* = 112	*n* = 113
Which of the following tests is most suitable for the diagnosis of suspected HAE patient? (Q3)						
Complement system	437 (63.2)	129 (54.2)	88 (80.0)	83 (69.7)	82 (73.2)	55 (48.7)
Hemostatic system	17 (2.5)	8 (3.4)	2 (1.8)	4 (3.4)	0 (0.0)	3 (2.7)
Non-specific allergy	140 (20.2)	62 (26.1)	13 (11.8)	15 (12.6)	20 (17.9)	30 (26.5)
Brain natriuretic peptide	10 (1.4)	4 (1.7)	5 (4.5)	0 (0.0)	0 (0.0)	1 (0.9)
Collagen diseases markers (e.g., antinuclear antibodies)	88 (12.7)	35 (14.7)	2 (1.8)	17 (14.3)	10 (8.9)	24 (21.2)
What is the most important item to ask in the interview? (Q5)						
Family history	353 (51.0)	103 (43.3)	73 (66.4)	72 (60.5)	63 (56.3)	42 (37.2)
Medication history	54 (7.8)	23 (9.7)	10 (9.1)	7 (5.9)	6 (5.4)	8 (7.1)
Disease history	121 (17.5)	43 (18.1)	10 (9.1)	23 (19.3)	14 (12.5)	31 (27.4)
Hospitalization history	9 (1.3)	2 (0.8)	0 (0.0)	1 (0.8)	3 (2.7)	3 (2.7)
Allergy history	155 (22.4)	67 (28.2)	17 (15.5)	16 (13.4)	26 (23.2)	29 (25.7)
How do you follow the patient? (Q6)						
Hospitalization and follow-up in my department	155 (22.4)	52 (21.8)	40 (36.4)	33 (27.7)	26 (23.2)	4 (3.5)
Hospitalization and referral to another department	301 (43.5)	98 (41.2)	31 (28.2)	52 (43.7)	51 (45.5)	69 (61.1)
Send her home for now but tell her to go to another outpatient department for a closer examination.	155 (22.4)	59 (24.8)	15 (13.6)	18 (15.1)	26 (23.2)	37 (32.7)
Send her home for now and follow up again as an outpatient in my department	76 (11.0)	27 (11.3)	22 (20.0)	15 (12.6)	9 (8.0)	3 (2.7)
Send her home for now and tell her to see a doctor if she has any symptoms again (no follow-up)	5 (0.7)	2 (0.8)	2 (1.8)	1 (0.8)	0 (0.0)	0 (0.0)
Knowledge of complement system and diagnostic rates of suspected HAE patients						
⇒selected C4 and C1-INH activity	131 (18.9)	30 (12.6)	38 (34.5)	27 (22.7)	24 (21.4)	12 (10.6)
⇒selected C4 and other complement system	180 (26.0)	45 (18.9)	42 (38.2)	33 (27.7)	34 (30.4)	26 (23.0)
⇒selected C1-INH activity and other complement system	339 (49.0)	96 (40.3)	79 (71.8)	71 (59.7)	64 (57.1)	29 (25.7)
⇒Unselected C4 or C1-INH activity	49 (7.1)	18 (7.6)	5 (4.5)	6 (5.0)	8 (7.1)	12 (10.6)

Abbreviations: AE, Angioedema; HAE, Hereditary Angioedema; C1-INH, C1 esterase inhibitor; C4, complement C4.

emergency physicians may be attributable to activities related to disease training. For example, resident pediatricians are required to study angioedema as part of society-certified training sessions. Emergency physicians also have the opportunity to study HAE because problems related to HAE are sometimes included in specialist exams and are presented in lectures in academic societies. In the case of young physicians, the fact that there was one question about HAE on the 99th National Medical Examination may have promoted knowledge and awareness about it. However, awareness of HAE among young physicians graduated after 4-9 years was not significantly higher than that of over 10 years generations, indicating that adding only one question to the National Medical Examination was not sufficient to disseminate knowledge among young physicians. Given these results, study questions on examinations and academic seminars for different physician specialties may be effective in disseminating disease knowledge of HAE.

TABLE 4 Diagnosis experience of HAE and indication/symptom awareness

	No. (%) respondents					
	Total	Internal medicine	Dermatology	Pediatrics	Emergency medicine	Gastroenterological surgery
	n = 692	*n* = 238	*n* = 110	*n* = 119	*n* = 112	*n* = 113
Diagnosis experience of HAE (have seen a suspected case)						
Have seen a suspected case and diagnosed as such	100 (14.5)	31 (13.0)	30 (27.3)	17 (14.3)	16 (14.3)	6 (5.3)
Have seen a suspected case, but diagnosed otherwise	142 (20.5)	34 (14.3)	40 (36.4)	32 (26.9)	24 (21.4)	12 (10.6)
Have seen a suspected case and referred them to another physician	131 (18.9)	54 (22.7)	18 (16.4)	14 (11.8)	37 (33.0)	8 (7.1)
Never seen such case	319 (46.1)	119 (50.0)	22 (20.0)	56 (47.1)	35 (31.3)	87 (77.0)
Diagnosis experience of HAE						
Treat the patient by myself	127 (18.4)	29 (12.2)	44 (40.0)	29 (24.4)	23 (20.5)	2 (1.8)
Referral to hematology department	79 (11.4)	25 (10.5)	2 (1.8)	13 (10.9)	19 (17.0)	20 (17.7)
Referral to dermatology department	99 (14.3)	28 (11.8)	40 (36.4)	6 (5.0)	18 (16.1)	7 (6.2)
Referral to allergy department	224 (32.4)	94 (39.5)	20 (18.2)	41 (34.5)	37 (33.0)	32 (28.3)
Referral to general medical department	119 (17.2)	50 (21.0)	4 (3.6)	15 (12.6)	20 (17.9)	30 (26.5)
Referral to collagen/rheumatology department	233 (33.7)	104 (43.7)	9 (8.2)	37 (31.1)	32 (28.6)	51 (45.1)
Referral to respiratory department	8 (1.2)	4 (1.7)	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.9)
Referral to nephrology department	20 (2.9)	10 (4.2)	1 (0.9)	3 (2.5)	3 (2.7)	3 (2.7)
Referral to other departments	17 (2.5)	4 (1.7)	0 (0.0)	3 (2.5)	4 (3.6)	6 (5.3)
Indication/symptom awareness[a]						
Subcutaneous edema	544 (78.6)	181 (76.1)	100 (90.9)	103 (86.6)	90 (80.4)	70 (61.9)
Laryngeal edema	557 (80.5)	188 (79.0)	95 (86.4)	107 (89.9)	101 (90.2)	66 (58.4)
Abdominal pain	426 (61.6)	133 (55.9)	72 (65.5)	88 (73.9)	83 (74.1)	50 (44.2)
Swelling after tooth extraction	139 (20.1)	40 (16.8)	35 (31.8)	23 (19.3)	26 (23.2)	15 (13.3)
Swelling of the tongue	380 (54.9)	115 (48.3)	71 (64.5)	70 (58.8)	84 (75.0)	40 (35.4)
Answers only	20 (2.9)	3 (1.3)	3 (2.7)	5 (4.2)	8 (7.1)	1 (0.9)
An answer containing all the correct answers	91 (13.2)	21 (8.8)	28 (25.5)	17 (14.3)	16 (14.3)	9 (8.0)
Answer some of the correct answers	636 (91.9)	217 (91.2)	110 (100)	115 (96.6)	110 (98.2)	84 (74.3)

Abbreviation: HAE, Hereditary Angioedema.

[a]Choice of correct symptoms of HAE are shown.

Disease awareness by region was also evaluated in the study The results shown in Table S4 suggest that there may be regional differences in the awareness of HAE. The proportion of physicians who selected an answer including C1-INH was higher in the Hokkaido, Kanto, Kinki areas, and lower in the Tohoku, Chubu, Chugoku, Shikoku, and Kyushu and Okinawa areas than the result in total. However, as the recruitment process did not consider the number of physicians or the proportions of doctors from the targeted departments from each region, these results do not necessarily accurately represent the level of HAE awareness. The results may differ if the departments, years of graduation from the academic institutions, and number of physicians were normalized by region. On the other hand, the difference in numbers and characteristics of the participants may reflect the medical situations in the area, thus explaining regional differences to an extent. Considering that HAE is a rare disease, this regional difference maybe generally applicable

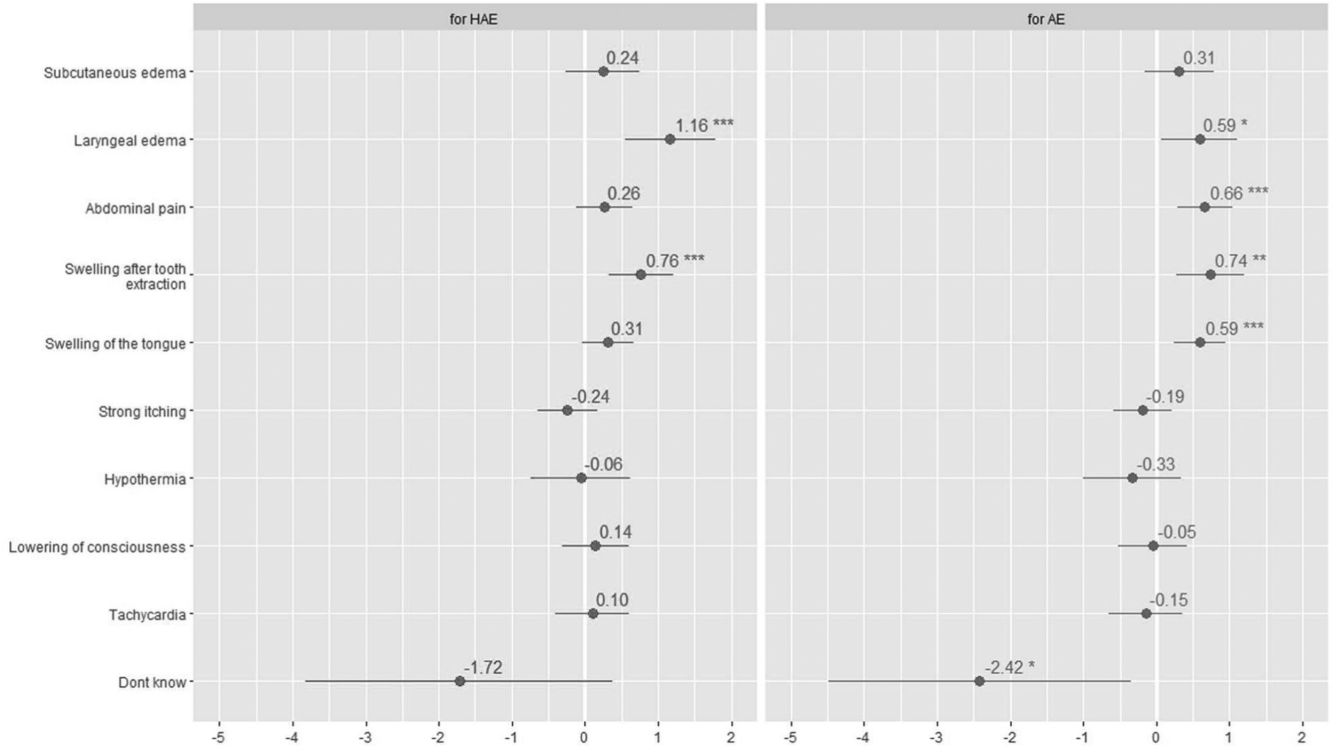

FIGURE 3 Relationship between diagnostic accuracy of AE and HAE and knowledge of symptoms of HAE. Logistic regression analysis of factors relating to relationship between diagnostic accuracy of AE and HAE and knowledge of symptoms of HAE. Significance codes: *** = 0.001, ** = 0.01, * = 0.05. Relevant choices for HAE: Subcutaneous edema, Laryngeal edema, Abdominal pain, Swelling after tooth extraction, swelling of the tongue. Irrelevant choices for HAE: Strong itching, hypothermia, Lowering consciousness, tachycardia. AE, Angioedema; HAE, Hereditary Angioedema

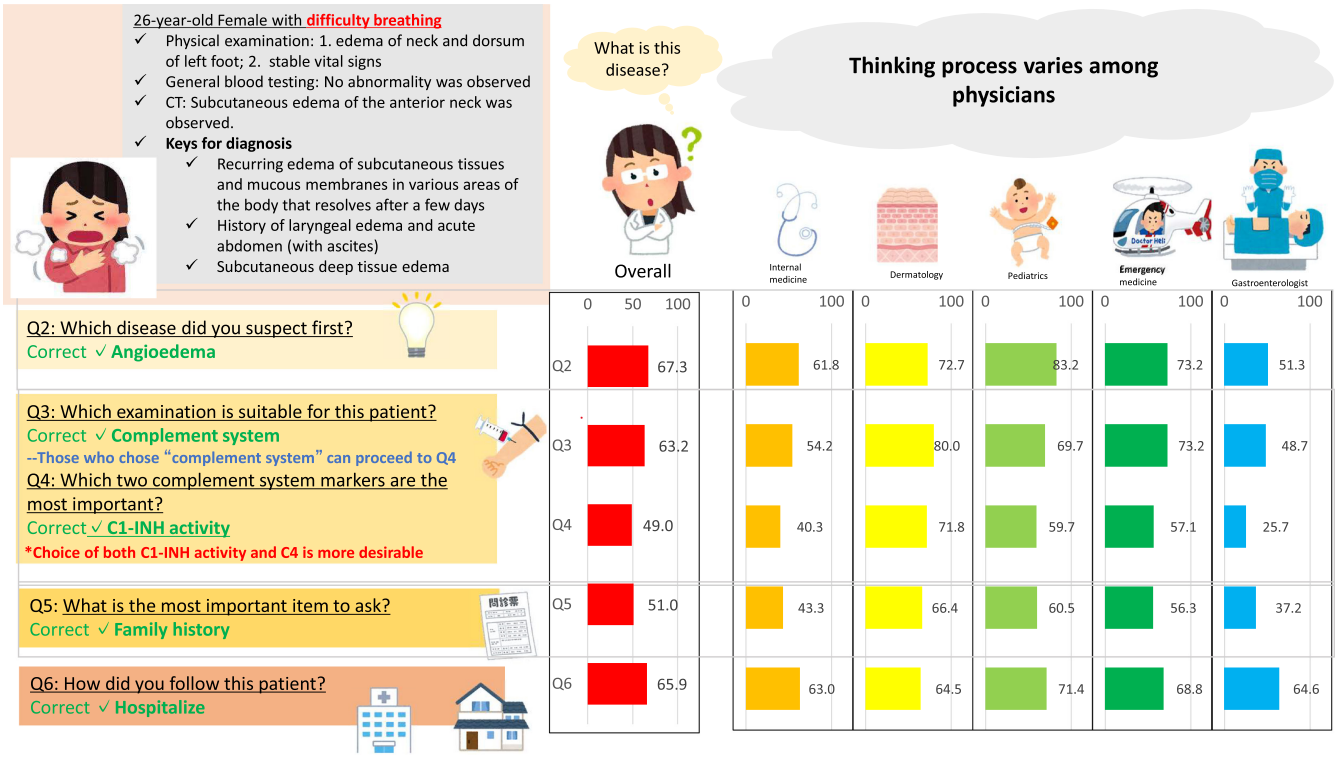

FIGURE 4 Physicians' thinking process when consulting a suspected HAE patient based on case-scenario. CT, computed tomography; C1-INH, C1 esterase inhibitor; C4, complement C4. Translation of Japanese characters in the figure: 問診票: medical interview sheet

to other rare diseases as well. One solution to help eliminate the regional differences might be to raise awareness of the disease on a regional basis, including establishment of a medical referral system connecting doctors to AE specialists in their region for the diagnosis and treatment of AE.

Measurement of C1-INH activity is critical for HAE diagnosis, and we measured knowledge of complement system among physicians seeing a suspected HAE patient. Overall, approximately 60% of physicians were able to utilize the case information for the measurement of complement levels essential for HAE diagnosis (Q3; Tables 3 and S1). Delayed diagnosis in HAE patients is presumed to occur because the disease cannot easily be distinguished from AE resulting from other causes or other acute diseases.[10] Among physicians who were able to select AE in case-scenario as the correct answer option, most physicians were able to select complement proteins as an appropriate answer. However, among them a lower percentage of physicians who could measure complement proteins (approximately 70%) selected C1-INH activity, with an even lower percentage selecting C4. In addition, approximately 30% of physicians, even specialized dermatologists, could not select the proper response to measure C1-INH activity (Table 3). In the Q7 keyword question (Table S1), physicians who chose correct answers (either HAE or idiopathic angioedema) were similarly divided between HAE and idiopathic angioedema, which shows similar symptoms to HAE and is difficult to differentially diagnose from HAE only from symptoms. Considering these results, it is imperative to raise awareness that measurement of C1-INH activity is necessary for the diagnosis of angioedema patients with suspected HAE.

Many physicians selected allergic diseases in both case-scenarios and keyword questions in this study. It is true that histaminergic edema and bradykinin-mediated edema are difficult to distinguish clinically.[11] However, since diagnostic treatments such as adrenaline, steroids, and antihistamines used to treat anaphylaxis are ineffective for HAE, it is reasonable that physicians consider the possibility of HAE when a patient with dyspnea has failed diagnostic treatment for allergic disease.[12]

Multivariate analysis to evaluate the relationship between knowledge of HAE symptoms and diagnosis of HAE showed that the four symptoms significantly associated with an answer option of "strongly suspect" AE in the case-scenario (Q1; Table S1) were laryngeal edema, swelling after tooth extraction, abdominal pain and swelling of the tongue, all of which are important symptoms of HAE as well. The three most commonly affected anatomical sites of HAE are the skin (skin attacks), the digestive tract (gastrointestinal attacks), and the upper airways. In a retrospective study of 221 patients, swelling of the skin was observed in 97% of 131,110 episodes of angioedema.[13] Swelling of the larynx may occur alone or in association with swelling of the lips, tongue, uvula, or soft palate.[13] Two of the AE symptoms, laryngeal edema, and swelling after tooth extraction that are widely used as textbook keywords for HAE were significantly associated with an answer option of "strongly suspect" HAE. However, considering that all four of the major symptoms of HAE were significantly associated with strong suspicion of AE, it can be assumed that physicians who are knowledgeable about AE are those who have sufficient knowledge of HAE.

One challenge for patients with HAE is unnecessary laparotomy. Considering the low awareness of HAE among gastroenterological surgeons, it might be necessary to educate HAE patients themselves about abdominal pain. In addition, if test results or CT findings differ from those of peritonitis, the possibility of HAE should be considered, and more attention should be paid. Patients with HAE were shown to be 2.5 times more likely to undergo abdominal surgery, including gynecological and urological surgery, than those without HAE.[14] Considering the low awareness of gastroenterological surgeons in this study, further education of these specialists is strongly recommended.

The limitations of this study are as follows: First, the data were collected from physicians who were members of Nikkei-BP panel and noticed this survey. Therefore, selection bias needs to be considered. Second, confirmation bias on data interpretation needs to be acknowledged. Third, this study was not a statistical analysis based on hypothesis setting but was descriptive and not statistically verified. Fourth, participants who are more aware of HAE might have sensed that this survey is about HAE and that certain choices given were dummy answers, which may have prompted them to choose certain answers. Fifth, there may also be hidden confounding factors between the departments or age groups and disease awareness. Lastly, there was no coordinated validation of intergroup differences in disease awareness. Therefore, the power of detection was not considered in the stratified analysis that was subdivided in the study.

HAE patients are often left undiagnosed for years due to a general lack of knowledge about the disease. Awareness of HAE among physicians can lead not only to early diagnosis but also to the elimination of unnecessary and invasive diagnoses and treatments. This study revealed that there were differences in the levels of awareness about HAE among the physicians in different specialties. The results imply the importance of awareness-raising activities such as academic seminars and medical specialty examinations. Understanding the importance of complement blood test for HAE, recognizing the life-threatening airway symptoms for HAE including laryngeal edema, swelling after tooth extraction, and swelling of the tongue, and having basic knowledge about abdominal pain which could be easily misdiagnosed as acute abdomen may lead to suspect AE when consulting patients with AE-like symptoms which consequently leads to differential diagnosis of HAE from AE.

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CONFLICT OF INTEREST

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DECLARATION SECTION

Approval of the research protocol: The study protocol was approved by the Non-Profit Organization MINS Institutional Review Board (Approval No. MINS-IRB 200244).

Informed consent: Informed consent was obtained from all participating physicians electronically.

Registry and the registration no.: UMIN-CTR, UMIN000042800.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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