Isao Ohsawa¹,², Daisuke Honda², Yuya Nakamura¹, Hiromichi Gotoh¹, Yoshikazu Goto¹, Yusuke Suzuki² and Yasuhiko Tomino³

¹Division of Nephrology, Internal Medicine, Saiyu Soka Hospital, Saitama, Japan
²Division of Nephrology, Department of Internal Medicine, Juntendo University Faculty of Medicine, Tokyo, Japan
³Asian Pacific Renal Research Promotion Office, Medical Corporation SHOWAKAI, Tokyo, Japan

Received: 04 September, 2018
Accepted: 12 September, 2018
Published: 14 September, 2018

*Corresponding author: Isao Ohsawa, M.D., Ph.D., Division of Nephrology, Internal Medicine, Saiyu Soka Hospital, T-7-22, Matsubara, Soka, Saitama, #344-0041, Japan, Tel: +81-944-6111; Fax: +81-944-8080; E-mail: i.osawa@saiyuqai.com

Keywords: Hereditary angioedema; HAE; C1-inhibitor; C1-INH, angioedema; Mass media; Website; Early diagnosis

https://www.peertechz.com

Case Study

Mass media information can facilitate early diagnose of hereditary angioedema: Case series study

Abstract

**Background:** A patient's motivation for consulting a physician is paramount to the first steps of achieving an early diagnosis of hereditary angioedema (HAE). Understanding what triggers this motivation can help in the design of strategies to increase the number of visits to a specialist physician following early symptoms of HAE. The aim of the present study was to identify the reasons that led patients to seek the opinion of an HAE expert physician.

**Methods:** The number of patients who had visited a specialist outpatient clinic for HAE was determined. All patients were asked what motivated them to seek medical consultation. Clinical data and blood samples were collected to establish a diagnosis.

**Results:** Seventy patients visited the clinic within a 30-month period between August 2015 and January 2018. Seven of these patients were diagnosed with HAE. The main source of evidence that prompted the visit to the specialist clinic was websites (67.1%), followed by newspapers (15.7%) and information provided by the home doctor (14.2%). The number of patients per month increased after a rise in the number of publications about HAE in newspapers and websites.

**Conclusion:** Mass media publications are an efficient way to motivate patients to visit an HAE expert physician.

Abbreviations

ACE: Angiotensin Converting Enzyme; C1-INH: C1-Inhibitor; HAE: Hereditary Angioedema; Ig: Immunoglobulin; NPO: Non-Profit Organization; Nsaids: Non-Steroidal Anti-Inflammatory Drugs

Background

Angioedema is defined as localized and self-limiting edema of the subcutaneous and submucosal tissues resulting from a temporary increase in vascular permeability. Clinically, angioedema involves the skin, airway and gastrointestinal tract among other organs[1], and symptoms can arise from different pathological mechanisms [2]. Mast cells play a crucial role in the majority of cases of angioedema. Since mast cell degranulation elicits the release of various inflammatory mediators, such as histamine, leukotrienes and prostaglandins, mast cell-mediated angioedema is usually controlled with anti-histamines or corticosteroids. Drug–induced angioedema can occur as a side-effect of treatment with angiotensin converting enzyme (ACE) inhibitors as they block the degradation of bradykinin. In addition, some patients who regularly use non-steroidal anti-inflammatory drugs (NSAIDs) may also present with angioedema (NSAIDs intolerance) [3]. Acquired angioedema, which is primarily observed in adult and elderly patients, is associated with lymphoproliferative disorders that produce auto–antibodies against C1–inhibitor (C1-INH) [4]. In addition, immune complexes and cryoglobulins can directly activate the classical pathway resulting in the consumption of C1-INH [5,6]. Since C1–INH is a strong inhibitor of activated factor XII and plasma kallikrein [7], decreased C1–INH function or plasma levels leads to excessive bradykinin production, which increases vascular permeability resulting in angioedema.

Hereditary angioedema (HAE) type I and II is a potentially life-threatening rare disease that results from mutations of the gene encoding C1-INH. Although HAE has been recognized as a Japanese Intractable Disease, our previous Japanese survey confirmed that the time to diagnosis was unacceptably long, being more than 13 years[8]. Plasma derived C1–INH concentrate has been the only drug available through the Japanese healthcare system for 25 years. Since clinical trials of subcutaneous self-administration of icatibant for acute attacks, and intravenous administration of icatibant for acute attacks, and intravenous

Citation: Ohsawa I, Honda D, Nakamura Y, Gotoh H, Goto Y, et al. (2018) Mass media information can facilitate early diagnose of hereditary angioedema: Case series study. Glob J Medical Clin Case Rep 5(2): 019-022. DOI: http://dx.doi.org/10.17352/2455-5282.000063
self-administration of plasma derived C1-INH for long-term prophylaxis have been completed, these drugs are likely to be approved in the near future in Japan. Once these therapies are approved, the goal of disease management in Japan will shift from the control of acute attacks to the improvement of HAE patients’ quality of life.

In contrast to lifestyle-related diseases such as diabetes, hypertension or hyperlipidemia, HAE cannot be diagnosed through yearly health checkups. Thus, an accurate diagnosis is dependent in part on the knowledge of the consulting physician. Physicians and other healthcare professionals have been educated on the distinct symptoms and laboratory findings associated with HAE [8,9], therefore, in order to achieve a prompt and accurate diagnosis of the disease, it is critical we understand how to encourage patients to visit an expert. In the present study, we explored what motivated patients to visit a specialist outpatient clinic for HAE.

Methods

The HAE outpatient clinic in the Saiyu Soka Hospital (Saitama, Japan) was established in August 2015 and information about the clinic was simultaneously published on the hospital website. The number of patients who visited the clinic between August 2015 and January 2018 was determined; all patients were asked what had motivated them to seek consultation at the HAE clinic.

All patients had a confirmed diagnosis of angioedema from their own photographs of the angioedema site(s) and/or referrals from their general physician. Additional information on the patient’s past medical history, including age of angioedema onset, family history of angioedema and location of past angioedema episodes, was collected. In particular, past symptoms of acute or chronic urticaria, prodromal of past angioedema episodes, was collected. In particular, past symptoms of acute or chronic urticaria, prodromal erythema marginatum, effectiveness of antihistamines and/or past symptoms of acute or chronic urticaria, prodromal of past angioedema episodes, was collected. In particular, past symptoms of acute or chronic urticaria, prodromal erythema marginatum, effectiveness of antihistamines and/or corticosteroids, estrogen–induced angioedema, menstruation-related angioedema, and habitual drug use were recorded.

At the first consultation, blood samples were obtained from all patients under normal conditions, and laboratory data for white blood cells, eosinophils, red blood cells, hemoglobin, hematocrit, serum creatinine, total protein, albumin, immunoglobulin (Ig) G, IgM, IgA, and IgE, cryoglobulin, C3, C4, and C-reactive protein were collected. For differential diagnosis, serum concentration of immune complex (using a C1q-binding assay) and anti-nuclear antibody were evaluated. Functional levels of C1-INH were determined using a chromogenic assay (Sysmex, Hyogo, Japan).

Diagnosis of HAE was confirmed using the diagnostic criteria described by Agostoni et al.[10], in addition to the Japanese guidelines published in 2010 [11]. Within these guidelines, the major clinical criteria are: (1) self-limiting, non-inflammatory subcutaneous angioedema without major urticarial rash, often recurrent and often lasting more than 12 hours; (2) self-limiting abdominal pain without clear organic etiology, often recurrent and often lasting more than 6 hours; and (3) recurrent laryngeal edema. Minor clinical criteria are a family history of recurrent angioedema and/or abdominal pain and/or laryngeal edema. Laboratory criteria include: (1) two separate recordings of C1-INH antigenic levels < 50% of normal in asymptomatic patients aged 12 months or older who had not recently received C1-INH infusions; (2) two separate recordings of C1-INH functional levels < 50% of normal in asymptomatic patients aged 12 months or older who had not recently received C1-INH infusions; and (3) a mutation in the C1 inhibitor gene that affects protein synthesis and/or function. Using this approach, HAE was diagnosed if there was evidence of one major clinical criterion and one laboratory criterion. Practical differential diagnosis was performed using distinct reference points for each angioedema (Figure 1).

Media publications and/or press releases about HAE in Japanese newspapers and websites were calculated from August 2015 to January 2018. Web articles containing the term “hereditary angioedema” were searched and pharmaceutical companies were requested to calculate their web articles. The numbers of media publications and/or press releases and the breakdown of patients’ diagnoses were analyzed per month.

The study was conducted in accordance with the Declaration of Helsinki (1995) and was approved by the Institutional Review Board at Saiyu Soka Hospital. Written informed consent was obtained from all participating patients.

Results

Up to January 2018, a total of 70 patients (male, n=21; female, n=49; mean age, 44.8±17.5 years) had visited the HAE outpatient clinic (Table 1). The age range was ‘0 to 19’ (7.1%) to ‘80 or older’ (1.4%). The most cited source that motivated patients to seek a consultation in the HAE outpatient clinic was websites (67.1%), followed by newspapers and information provided by home doctors, 15.7% and 14.2% respectively (Table 1). Two children (2.8%) were suspected and brought to the clinic by their father who had a diagnosis of HAE.

Five patients (7.1%) were excluded because their symptoms did not match the diagnostic criteria for angioedema (Table 2). These patients were diagnosed with heart failure, lymphedema and erythema based on their present and past medical history and skin examination. The dominant diagnosis was mast cell-mediated angioedema (45 patients; 64.2%). Drug-induced angioedema, idiopathic angioedema and NSAID intolerance were each less than 8% of cases (Table 2). A small number
of patients had a combination of two diagnosis such as mast cell-mediated angioedema plus drug-induced angioedema or idiopathic angioedema plus NSAID intolerance (4.3% and 1.4%, respectively). Seven (10%) patients were diagnosed with HAE (Table 3). Of these, five were adults and two were children who came from the same family. Three patients had an independent family history of angioedema. All HAE patients had low functional C1-INH levels and a low concentration of serum C4 (Table 3). The range of the interval from onset of symptoms to diagnosis was 0 to 55 years. Patient 5 was asymptomatic, and had not had an apparent onset of angioedema (Table 3).

The analysis of mass media publications identified five educational websites about HAE (Figure 2), including two non-profit organizations (NPO), “CREATE” (http://www.create2011.jp/message.html) and “HAEJ” (https://haej.org), one patient association, “Kumimu” (http://www.create2011.jp/kumimu/activity.html), and one website run by a pharmaceutical company, “HAE Information Center” (http://www.hae-info.jp). These websites were available before the start of our study. Another website established by a pharmaceutical company, “Hare-Fukutsuu NAVI” (https://www.harefukutsuu-hae.jp), went live in April 2017. These websites contained information on the typical symptoms and therapeutic options for HAE, and also linked to each other. The secretariats of “CREATE” and “HAEJ” introduced an HAE expert physician, while “HAE Information Center” and “Hare-Fukutsuu NAVI” listed the medical centers visited by HAE experts.

Twenty-three HAE articles were found in newspapers, of which 18 were in local newspapers and five were in national circulations. In addition, 64 web articles had been published; 35 articles were intended for medical professionals, 26 for the general public and three were on-line versions of printed newspaper articles. The timing of these publications clustered in two periods, the first from April to August 2016, and the second from February to June 2017. An increase in the number of visitors to the HAE outpatient clinic was observed after each of these clusters of publications and continued for 4–5 months (Figure 2). Particularly in the second period, the number of visitors increased during the launch of the new pharmaceutical company website, “Hare-Fukutsuu NAVI”. In general, no fewer than 1–2 patients per month visited the HAE outpatient clinic (Figure 2).

**Discussion**

To our knowledge, this is the first study that investigated the relationship between mass media information and diagnosis of HAE. The results showed that patients turn to mass media to search for information when suffering from unfamiliar symptoms. The study revealed that the majority of patients who visited the HAE outpatient clinic from August 2015 to January 2018 did so as a result of articles published in mass media, the majority of which were articles published on websites. The number of visiting patients increased during and after two clusters of publication of articles in newspapers and websites. Websites from NPOs, a patient association and pharmaceutical companies were a basic source of HAE information for the patients. Furthermore the publication of articles in newspapers or websites was a very effective tool to motivate patients to seek expert advice.

### Table 1: Patient characteristics and reasons for seeking consultation.

| Gender, n (%) | N=70 |
|--------------|------|
| Female       | 49 (70.0) |
| Male         | 21 (30.0) |
| Mean age, years (SD) | 44.8 (17.5) |
| Age group (years), n (%) |      |
| 0–19         | 5 (7.1) |
| 20–39        | 19 (27.2) |
| 40–49        | 31 (44.3) |
| 60–79        | 14 (20.0) |
| >80          | 1 (1.4) |
| Reason for seeking consultation, n (%) |      |
| Online search (website) | 47 (67.1) |
| Newspaper article | 11 (15.7) |
| Information by home doctor | 10 (14.3) |
| Recommendation by relatives with family history of HAE | 2 (2.9) |

HAE, hereditary angioedema; SD, standard deviation.

### Table 2: Patient diagnoses.

| Diagnosis                               | n (%) |
|----------------------------------------|-------|
| HAE                                    | 7 (10.0) |
| Mast cell-mediated angioedema           | 45 (64.3) |
| Drug-induced angioedema                 | 5 (7.1) |
| Mast cell-mediated + Drug-induced angioedema | 3 (4.3) |
| Idiopathic angioedema                   | 4 (5.7) |
| Idiopathic angioedema + NSAID intolerance | 1 (1.4) |
| Other                                   | 5 (7.1) |

HAE, hereditary angioedema; NSAID, non-steroidal anti-inflammatory drug.

### Table 3: Individual HAE patient demographics.

| Patient number | Age | Gender | Family history of angioedema | C1-INH function, % | C4‡, mg/dL | Interval from disease onset to diagnosis, years |
|----------------|-----|--------|-----------------------------|--------------------|-----------|---------------------------------------------|
| 1              | 65  | F      | No                          | <25                | 10        | 55                                          |
| 2              | 68  | F      | Yes                         | <25                | 3.7       | 43                                          |
| 3              | 52  | F      | Yes                         | <25                | 2.6       | 37                                          |
| 4              | 5   | M      | Yes                         | 34                 | 11.8      | 0                                           |
| 5              | 7   | F      | Yes                         | 34                 | 8.1       | asymptomatic                                |
| 6              | 42  | M      | No                          | 59                 | 13.7      | 20                                          |
| 7              | 39  | F      | Yes                         | <25                | 4.6       | 15                                          |

1Normal range: 50–140%; 2Normal range: 14–36 mg/dL; C1-INH, C1-inhibitor.
The first step to making an accurate diagnosis of HAE is to confirm the symptoms are certainly angioedema. Even though patients are unable to easily differentiate between angioedema and other dermatological conditions such as erythema, cardiac edema or varicosis, only a small proportion of patients who visited the outpatient clinic did not present with angioedema. Because educational websites include the typical symptoms of HAE, non-angioedema patients might be excluded prior to visiting the clinic.

A few patients (10%) were diagnosed with HAE. The early diagnosis of HAE facilitated the provision of a suitable medical environment to receive adequate therapy. Moreover, in some cases following the diagnosis, blood relatives were also tested for HAE. Since mass media reaches a broad population, it can be used effectively to increase awareness and education of rare diseases and to prompt patients to seek medical expert advice.

Except for the two pediatric patients, the period between onset of symptoms and HAE diagnosis was 15–55 years. This is congruent with previous Japanese studies reporting a highly variable delay between symptom onset and diagnosis[8, 12]. The estimated prevalence of HAE is 1 in 50,000 people, with no reported differences among different ethnic groups [13]. Accordingly, in Japan an estimated 2,000 to 3,000 people will have HAE. However, unofficial data from several pharmaceutical companies showed that the number of diagnosed HAE cases are estimated to be only 470. Therefore, there is an unmet need to design efficient strategies to identify those with HAE.

The main limitation of this study is that the laboratory test of C1–INH and Cq4 antigenic levels is not approved by the Japanese healthcare system and is not routinely performed to diagnose HAE. Although, the Agostoni’s diagnostic criteria[10] is valid without testing for antigenic C1–INH levels, in recent guidelines, low Cq4 level is listed as an exclusion criterion for acquired angioedema [13]. HAE patients often present with low Cq4 levels [14], however, this does not always exclude acquired angioedema.

Since our single-center survey was carried out, a total of four additional outpatient clinics for HAE have been established. These patient–centered initiatives may stimulate an improved environment for HAE patients.

Conclusion

Mass media publications are an efficient way to motivate patients to visit an HAE expert physician.

Acknowledgements

We wish to thank colleagues in the Department of Internal medicine, Saiyu Soka Hospital, Saitama, Japan. We also wish to thank Meridian HealthComms for providing editorial assistance with this manuscript, funded by CSL Behring.

Funding

This work was supported by JSPS KAKENHI Grant Number 17K15783.

References

1. Zuraw BL. (2008) Clinical practice. Hereditary angioedema. New Eng J Med 359: 1027-1036. Link: https://goo.gl/29heGT
2. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, et al. (2010) 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol 6: 24. Link: https://goo.gl/rgCndR
3. Assero R, Babvek S, Blanca M, Blanca-Lopez N, Cortellini G, et al. (2013) Clinical management of patients with a history of urticaria/angioedema induced by multiple NSAIDs: an expert panel review. Int Arch Allergy Immunol 160: 126-133. Link: https://goo.gl/Jfr0V
4. He S, Tsang S, North J, Chohan N, Sim RB, et al. (1996) Epitope mapping of C1 inhibitor autoantibodies from patients with acquired C1 inhibitor deficiency. J Immunol 156: 2009-2013. Link: https://goo.gl/3WJCs
5. Cicardi M, Biasini G, Cugno M, Spalth P, Agostoni A. (1993) Autoimmune C1 inhibitor deficiency: report of eight patients. Am J Med 95: 169-175. Link: https://goo.gl/b6bPQ4
6. CasalP, BorziniP, PiolettiP, InvernizziF, ZanzuS (1978) Acquired C1-Inhibitor Deficiency in Essential Cryoglobulinemia and Maccrocryoglobulinemia. Acta haematol 59: 277-284. Link: https://goo.gl/q4YfTT
7. Ghannam A, Defendi F, Charignon D, CospaF, Favier B, et al. (2013) Contact system activation in patients with HAE and normal C1 Inhibitor function. Immunol Allergy Clinics 33: 513-533. Link: https://goo.gl/Sot3Zn
8. Ohsawa I, Honda D, Nagamachi S, Hisada A, Shimamoto M, et al. (2015) Clinical manifestations, diagnosis, and treatment of hereditary angioedema: survey data from 94 physicians in Japan. Annals of Allergy, Asthma & Immunology 114: 492-498. Link: https://goo.gl/N9F1LJ
9. Ohsawa I, Honda D, Hisada A, Inoshita H, Onda-Tsueshita K, et al. (2018) Clinical Features of Hereditary and Mast Cell-mediated Angioedema Focusing on the Differential Diagnosis in Japanese Patients. Intern Med 57: 319-324.
10. Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, et al. (2004) Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 114: S51-S131. Link: https://goo.gl/7FLJK5
11. Horiuichi T, Ohi H, Ohsawa I, Fujita T, Matsushita M, et al. (2012) Guideline for hereditary angioedema (HAE) 2010 by the Japanese Association for Complement Research - secondary publication. Allergol int 61: 559-562. Link: https://goo.gl/coc1EY
12. Yamamoto T, Horiuichi T, Miyahara H, Yoshizawa S, Maehara J, et al. (2012) Hereditary angioedema in Japan: genetic analysis of 13 unrelated cases. Am J Med Sci 343: 210-214. Link: https://goo.gl/JRLVcj
13. Maurer M, Magerl M, Ansotegui I, Aygören-Pursen E, Betschel S, et al. (2018) The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy 73: 1575-1596. Link: https://goo.gl/59oQwN
14. Honda D, Ohsawa I, Sato N, Inoshita H, Mano S, et al. (2017) Diminished capacity of opsonization and immune complex solubilization, and detection of anti-C1q antibodies in sera from patients with hereditary angioedema. Allergol Int 66: 603-609. Link: https://goo.gl/43dwBP