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Original Article

A questionnaire-based survey to evaluate and improve the current HHT medical and social condition in Japan

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Received : 24 April 2020
Accepted : 03 August 2020
Published : 02 October 2020

DOI
10.25259/SNI_211_2020

Quick Response Code:

ABSTRACT

Background: Hereditary hemorrhagic telangiectasia (HHT) is a genetic systemic vascular disease affecting multiple organs and shows recurrent intractable symptoms. This disease has not been widely recognized in Japan until recently. Both diagnosed HHT patients and potential ones have faced difficulties because of the unfamiliarity with the disease in Japan. To evaluate the effect and degree of such a Japanese situation, a questionnaire-based survey was executed in this study.

Methods: This survey was carried out among the members of HHT Japan Association. The organization consisted of 102 members (as of 6/2019), mainly HHT patients and their family members. A questionnaire was used to gather demographic data, the effort to reach the diagnosis, and information regarding current patients' and their families' medical managements.

Results: Of the 102 questionnaires distributed, we have got 56 responses. The participants were mostly female (30) with an average age of 55.4 ± 14.8 (mean ± standard deviation [SD]) years. The average age of males was 53.5 ± 16.4. Relatively many HHT patients were born in huge cities such as Tokyo, Osaka, and Fukuoka Prefecture (n = 4 to 8 patients). The duration between the initial symptoms and the definite diagnosis was 8.8 ± 10.9 years. The number of hospitals involved in the final diagnosis was 2.38 ± 1.83. More than 70% of patients now have to visit at least two departments and 24% of HHT patients did not want their family to screen for HHT.

Conclusion: HHT medical practice in Japan should be further modified, for example, by establishing HHT centers and educating primary care physicians and HHT patients.

Keywords: Epistaxis, Hereditary hemorrhagic telangiectasia, Osler–Weber–Rendu disease, Quality of life

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu disease, is a genetic systemic vascular disease characterized by prominently recurrent epistaxis, cutaneous spot (telangiectasia), and arteriovenous shunt lesions in multiple organs.[7] This systemic vascular disorder was presumed to be extremely rare in Japan until the recent epidemiological survey showed that 1 out of 5000–8000 Japanese suffered from HHT.[2] In the report of Ministry of Health, Labour and Welfare in 2017, only 445 HHT patients were specified as "incurable" by Ministry of Health, Labour and Welfare (No. 227).[19] This figure is much smaller than the estimated number of HHT patients in Japan. It is possible that many patients with trivial symptoms or asymptomatic HHT could be overlooked or misdiagnosed. Furthermore, according

to the previous studies carried out in other countries, the diagnosis of HHT patients is reported to be delayed in many cases.[10,13] In the meantime, preventive interventions for particular types of lesions like pulmonary AV shunts have been strongly recommended in the International Guidelines for the Diagnosis and Management of HHT.[6] This is because concise and early definite diagnosis by screening for high-risk group (families of HHT patients) can help avoid critical events such as stroke or brain abscess and has been proven to extend the prognosis.[3,8,14]

In addition to the problem of potential HHT patients, diagnosed HHT patients also suffer from improper medical management due to disease's rarity and multisymptomatic features. HHT expresses frequent intractable epistaxis and affects multiple organs, which force the patient to visit multiple departments in different medical institutes. There are few literatures or surveys which demonstrated overall and detailed situations or demands of Japanese HHT patients. Through this study, we planned to evaluate the difficulty of HHT diagnosis, current situation of HHT patients, and the possibility to detect potential undiagnosed patient to combat the unrefined HHT clinical condition in Japan.

MATERIALS AND METHODS

This questionnaire-based survey was approved by the ethical committee of our hospital (No. 20190176) and distributed to the members of HHT Japan Association, a nonprofit organization founded in 2012, consisting of 102 members (as of 6/2019). The content of the questionnaire is shown in [Figure 1]. The paper-based questionnaire was sent to the all members of the HHT Japan Association.

RESULTS

Background

Out of the 102 questionnaires distributed among the patients, 56 responses were recorded, and females were found to be dominant (30). The average age of males was 53.5 ± 16.4 (mean ± standard deviation [SD]) and females was 55.4 ± 14.8 (mean ± SD). There were more HHT patients from large cities in Japan such as Tokyo, Osaka, and Fukuoka Prefecture (n = 4–8 patients). The other patients are distributed across Japan.

Difficulty of diagnosis

The most frequent symptom which compelled the patients to visit the hospital was epistaxis (50% of HHT patients) and the second most frequent one was neurological deficit [Figure 2a]. The mean age of the patients who visited hospitals was 40.1 ± 15.6 (mean ± SD) [Figure 2b]. The duration between the initial symptoms and the final diagnosis was 8.8 ± 10.9 years [Figure 2c]. The number of hospitals required for the final diagnosis was 2.38 ± 1.83 [Figure 2d].

the patient's age
the patient's sex
the patient's birthplace
the symptom which made the patients visit hospitals
the age when the patient noticed the symptoms and at the time of HHT diagnosis
the duration of time between initial symptom and the diagnosis
the number of hospitals which required the final diagnosis
the frequency of nasal bleeding
the number of departments the patient routinely visits related HHT
what the patient hoped the doctor to do
the sensation of economic burden due to HHT
the obtain of the intractable disease certification by Japanese Ministry of Health
the consciousness that the family members frequently had nasal bleeding or not
the number of family members (the patients' parents, siblings and children)
the number of family members diagnosed as HHT
the intent to recommend the undiagnosed patients to visit the HHT outpatient
the reasons why the patient does not recommend their family's visit to HHT outpatient
the experience of genetic test

Figure 1: Questionnaire for hereditary hemorrhagic telangiectasia patients and their families.

Current situation of HHT patients

As for the current frequency of nasal epistaxis, 45% of HHT patients suffer from nasal bleeding every day. As much as, 90% of patients had epistaxis at least once a week [Figure 3a]. The number of departments the patients had to visit periodically related to HHT was 2.2 ± 0.9 (mean ± SD). More than 70% of patients visited at least two departments [Figure 3b]. About 60% of HHT patients experienced moderate economical oppression about HHT medical management [Figure 3c]. The proportion of the HHT patients who obtained Japanese Ministry of Health, Labour and Welfare-certificated intractable disease subsidiary was 57% [Figure 3d]. The patients' expectations of the HHT treatment were as follows: constant updates about the HHT therapy and convenient access to HHT-specific epistaxis treatment, the patients' expectations of the HHT treatment were as follows: constant updates about the HHT therapy, convenient access to HHT-specific epistaxis treatment, more consultation time, otolaryngologist's acquisition of expert skill and knowledge to stop the recurrent nasal bleeding, easy access to genetic testing, and receiving intractable disease certification from Japanese Ministry of Health, Labour and Welfare.

Potential HHT patients

Frequent nasal bleeding was noticed by family members for 82% of HHT patients [Figure 4a]. [Figure 4b] shows the number of patients diagnosed with HHT in a family other than the patient answering the current questionnaire. The average number of HHT patients in one family was 1.3 ± 1.3 individuals. In addition, there were 5.4 ± 1.2 (mean ± SD)

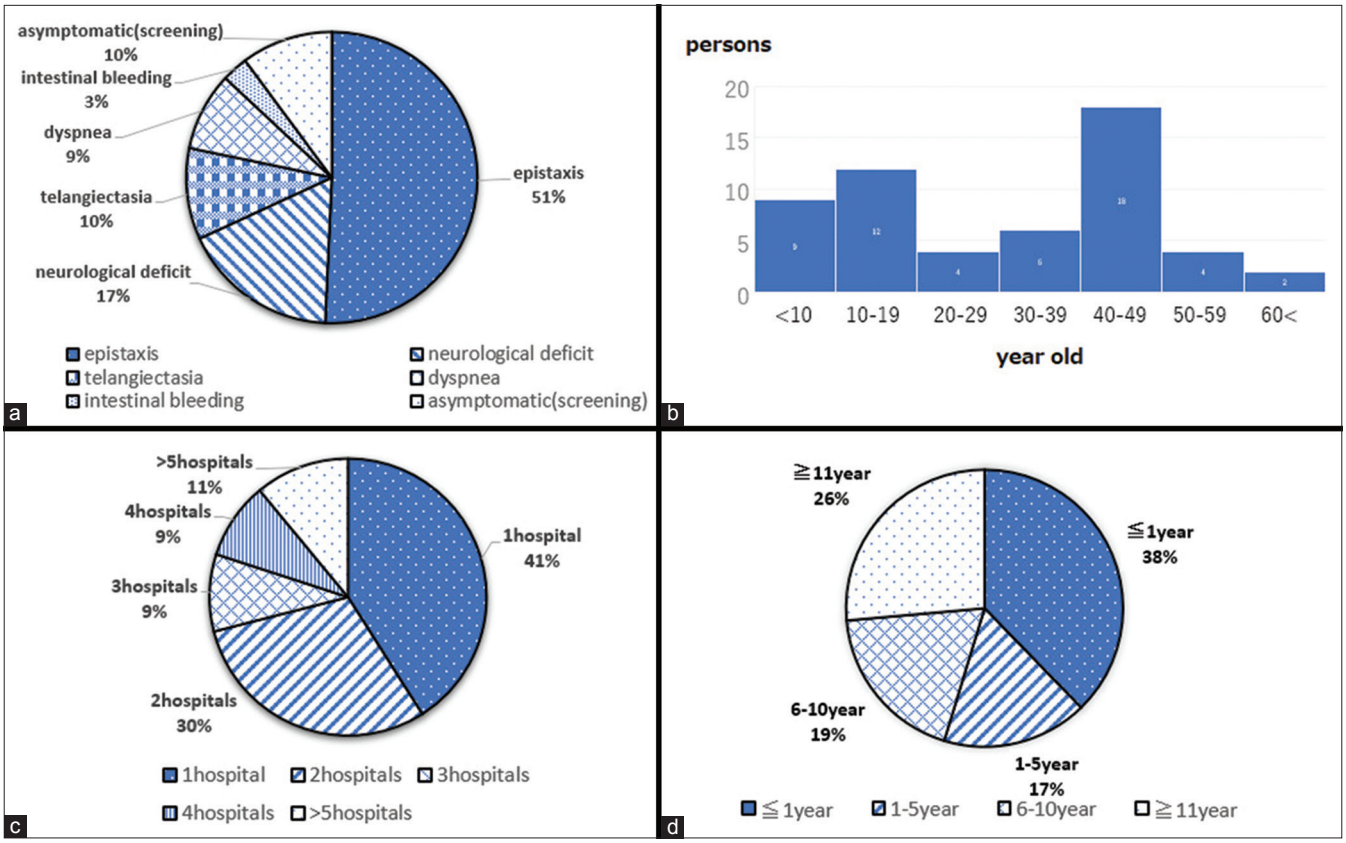

Figure 2: Symptoms and diagnosis of hereditary hemorrhagic telangiectasia (HHT). (a) Symptoms that compel patients to visit a hospital. (b) Age distribution of initial symptoms. (c) Number of hospitals required for HHT diagnosis. (d) Duration of HHT diagnosis.

persons in the family of an HHT patient. As much as, 24% of HHT patients did not want their family to consult a doctor for HHT. [Figure 4c] shows the reasons for the same. More than 65% of HHT patients felt that their family had no apparent symptoms, and therefore, they did not have to visit a doctor.

DISCUSSION

From our survey, current status of HHT medical practice in Japan was elucidated. It was found that to get a confirmed diagnosis of HHT, around 9 years and multiple times screenings in 2–4 hospitals were required as an average. Most patients face economical oppression and have to visit multiple departments to diagnose HHT in addition to the frequent physical anguishing symptoms such as recurrent and intractable nasal bleedings every day. The HHT patients' reluctance to recommend their family members to visit the doctor could be one of the major reasons why HHT patients have not been diagnosed adequately in Japan.

The road to early diagnosis

Epistaxis is a prominent symptom of HHT.[1,12] Up to their 40s, almost all HHT patients experienced recurrent nasal bleeding.[4] Around half of patients (45%) suffered from nasal bleeding every day [Figure 2b]. This figure matched with those in the previous literature.[6] In addition, nasal bleeding has been reported to critically influence the quality of life (QOL) of many HHT patients.[5] Such an importance and notable symptom could be highly helpful to diagnose HHT. However, in routine medical practice, clinicians encounter a number of patients complaining of epistaxis which is not associated with HHT. Moreover, most health-care providers have limited specific knowledge about HHT.[2,4,6,15,16] In our cohort, 40% of patients were diagnosed within 1 year of presenting the initial symptom and visited only one hospital. On the other hand, as many as 45% of patients took more than 5 years to be diagnosed with HHT. A definite diagnosis for HHT was received at the age of 40.1 ± 15.6 years. These figures are in agreement with those shown in the previous studies carried out in other countries such as Italy and China.[10,13] In those studies, the duration from disease onset to first definite diagnosis of HHT was more than 25 years. In addition, the age of definite diagnosis was 40.1 ± 17.2 years[10] which was very similar figure with ours. It is important to reduce the number of HHT patients who took more than 1 year to receive the diagnosis, which constitute 60% of patients in our study. To do so, adopting the Curacao

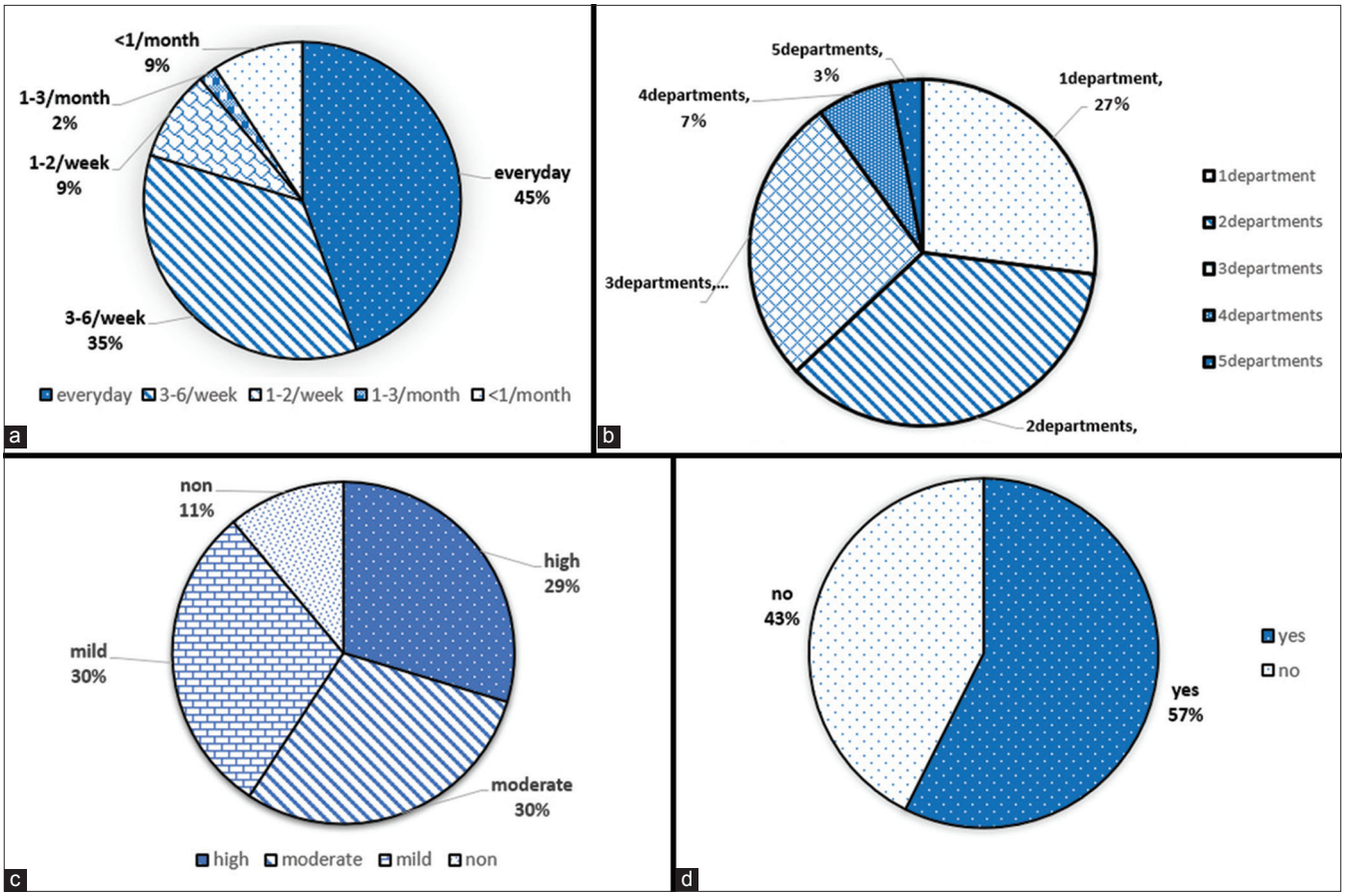

Figure 3: Current data of hereditary hemorrhagic telangiectasia (HHT) patients. (a) Frequency of epistaxis. (b) Number of departments patients has to visit. (c) Feeling of economical oppression among patients. (d) Proportion of HHT patients who are supported by Ministry of Health, Labour and Welfare.

diagnosis criteria[6] (1. recurrent epistaxis, 2. telangiectasia, 3. AV shunts in some organ systems, and 4. family history of HHT) is pertinent. We can suspect or rule out the adult HHT patients with simple questions and brief physical examination with this criterion. Especially for doctors who specialize otolaryngology, ED, and home medicine, this laconic yardstick should be memorized.

How to identify asymptomatic potential HHT patients

HHT is an autosomal dominant disease and the penetrance is almost 100% as the age of patients advanced.[1,18] Thus, in theory, 50% of family members could show some symptoms related HHT regardless of gender. From our result, only 1.3 ± 1.3 (mean ± SD) patients were diagnosed in a family (consisting of patients' parents, siblings, and children) of HHT patients. Our data showed that 5.4 ± 1.2 (mean ± SD) patients belong to one family. Considering autosomal dominancy and high penetrance, 2–3 persons in one family can be diagnosed with HHT, theoretically. This survey was carried out in a highly motivated group (HHT Japan Association members) as a target population. Even among such a group, the detection rate of HHT disease in their family was found to be low. In general, some young patients do not show any symptoms such as epistaxis or telangiectasia.[12] From our result, the most frequent reason why the HHT patients did not encourage their family members visit the doctor was that they were asymptomatic. This could increase the risk and could lead to poor functional or survival prognosis of undiagnosed family members. For asymptomatic potential HHT patients, especially young individuals, gene test can be performed. At present, mutations in three genes (endoglin, activin A receptor-like kinase 1, and Smad4) have been identified to be the cause of HHT.[11] Phenotypes, namely, symptoms or complications, are relatively different between them. In Japan, a genetic test can be performed in only 47 hospitals and is not covered by national medical insurance. Therefore, it is important that the doctors who treat HHT patients show the patient the importance of screening for high-risk HHT family members.

Future policy for HHT medical management in Japan

HHT shows a wide variety of symptoms because AV shunts are located in many organs such as the liver, intestine, spine,

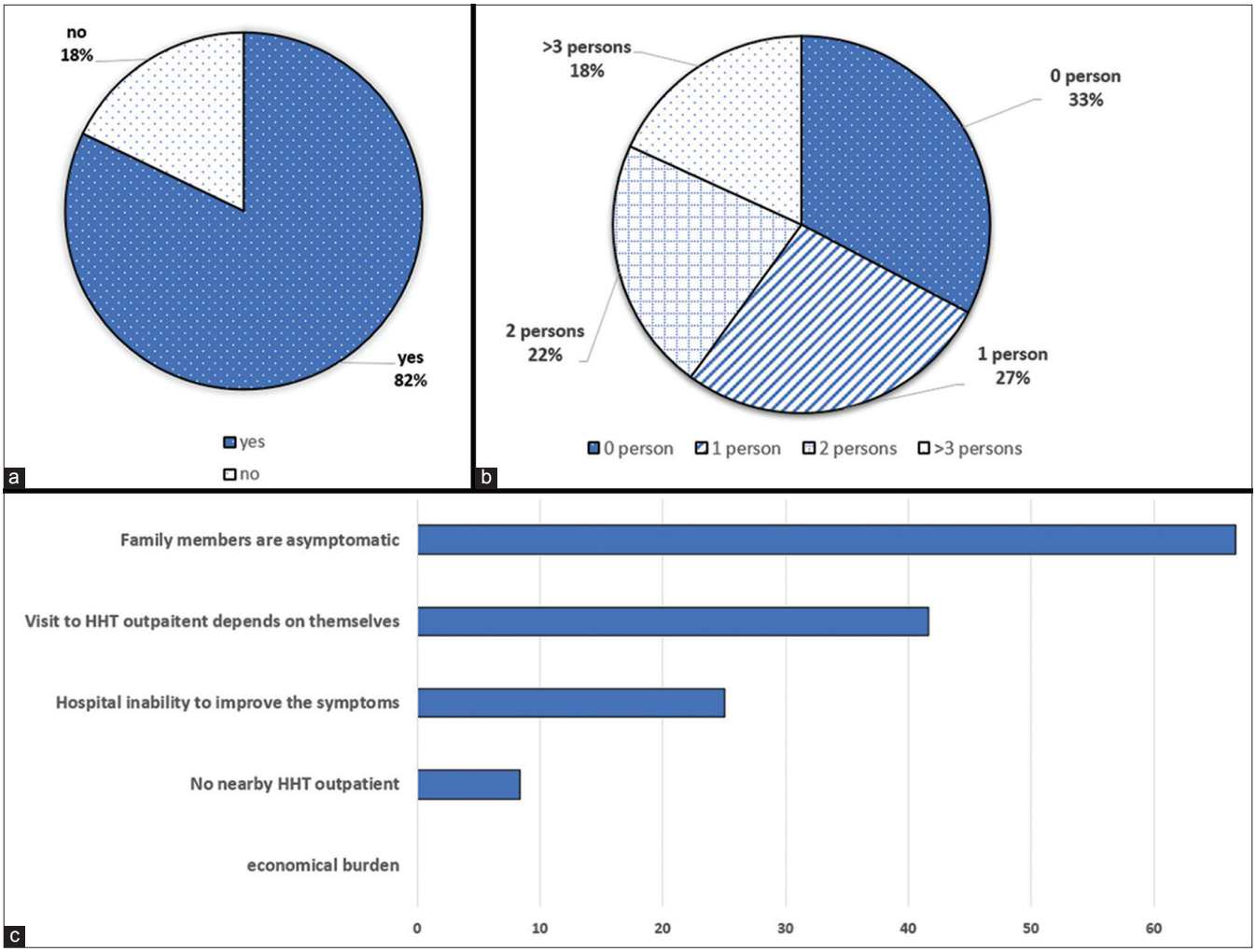

Figure 4: Data of potential hereditary hemorrhagic telangiectasia (HHT) patients. (a) Proportion of HHT patients who noticed epistaxis in family members. (b) Number of people diagnosed as HHT other than the patient. (c) Reasons why HHT patients do not want their family members not to visit the medical institution.

brain, and lungs. Stroke, brain abscesses, hematochezia, hematemesis, and heart failure can sometimes occur and require special treatment by experts.[17] It was observed that one out of three patients has to visit more than 3 kinds of departments related with HHT treatment. In addition, periodic medications such as nasal bleeding hemostats or systemic effective anti-angiogenesis drugs are currently required or will be required in near future. Thus, to alleviate the burden of a patient, it is better that high-volume hospitals harmonize the special departments related to HHT medical management and follow-up the HHT patients systematically as one team. In Japan, there were only a small number of hospitals which could accommodate patients with HHT and additionally they did not always have all necessary departments needed for the management of HHT-associated complications. Thus, the patient has to visit a very far general hospital or went to different kinds of clinics. Given the situation, HHT Japan Association was founded (2012) and the organization created a homepage[9] which listed the hospitals providing HHT medical practice. However, there are not enough hospitals in the list to be distributed evenly or from north to south appropriately. Like the USA, Japan should focus on HHT therapy and create HHT centers. As for treatment costs, 60% of patients feel more than moderate economic oppression as derived from the results of the study. In Japan, HHT has been assigned to the Japanese Ministry of Health, Labour and Welfare-certificated intractable disease (No. 227) which financially supports HHT patients and their families. However, 40% of HHT patients are not assigned to the Japanese Ministry of Health, Labour and Welfare-certificated intractable disease. This seems to be based on the number of doctors who can apply for the certification and difficult criteria. Therefore, for bettering the social status of HHT patients, it is suggested that the Japanese Government supports the construction of HHT centers and improves the criteria of Ministry of Health, Labour and Welfare-certificated intractable disease (No. 227) as it can help alleviate the time-

consuming long or frequent visits to outpatient department and economic burden of HHT patients.

There are several potential limitations to this study. The target of this survey is HHT Japan Association's members and the number of responses was limited. It may be difficult to generalize the study results to the HHT population for the management of the disease in Japan.

CONCLUSION

HHT medical practice in Japan should be further modified and advanced by implementing a social system such as HHT center establishment and education for primary care physicians as well as HHT patients. Such efforts would help alleviate patients' physical, psychiatric, and economical suffering and could improve the QOL of HHT patients. In addition, appropriate screening administration for potential patients may prolong the overall survival rate of HHT patients in Japan.

Acknowledgment

My sincere thanks to Dr. Komiyama who communicated with the members of HHT Japan and helped acquire the necessary data required for this study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Arai N, Akiyama T. A questionnaire-based survey to evaluate and improve the current HHT medical and social condition in Japan. Surg Neurol Int 2020;11:323.