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Nationwide epidemiological survey of superficial hemosiderosis in Japan

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ABSTRACT

Background: The Japanese guideline for diagnosis and classification of superficial hemosiderosis (SHS) has recently been published, for which patient medical expenses are supported by the Ministry of Health. We sought to clarify the clinical features, method of diagnosis, and treatment for SHS in Japan.

Methods: We sent a questionnaire survey to 792 medical institutes of the Japanese Society of Neurology, to collect information about SHS, including patients during 2017.

Results: We received replies from 287 institutes (36.2%). Estimated total number of patients with SHS in 2017 was 129 at 55 institutes. All patients were diagnosed by neurologists. Among 123 patients with available data, 81 patients (63%) had "classical" type (c-SHS), 29 (24%) had "localized" type (l-SHS), and 13 patients (10%) had "atypical" type (a-SHS). Five patients with l-SHS were excluded because of lacking detailed information. There were available data for the cause of SHS in 77 patients (63%): 55 (69%) with c-SHS, 16 (55%) with l-SHS, and 6 (48%) with a-SHS. Pharmacological or surgical treatment was given at 31 institutes. Medical expense subsidies were filed for 41% of patients.

Conclusions: Using the Japanese guideline for diagnosis of SHS, over 100 patients were confirmed as having SHS with characteristic clinical features. SHS is not a rare clinical condition in Japan.

1. Introduction

Superficial hemosiderosis (SHS) is considered a rare and progressive disease, but it is often difficult to make a precise diagnosis. The clinical symptoms of SHS are characterized by deafness and/or cerebellar ataxia that are observed in approximately 90% of patients with SHS [1]. In addition, cognitive disturbance is present in patients with SHS. The overall estimated population prevalence among individuals age 50–89 years is 0.56% [2]. Iron-sensitive magnetic resonance imaging (MRI) of the brain and spinal cord reveals hypointense lesions on the surface of the cerebrum, brainstem, cerebellum, and spinal cord (susceptibility-weighted imaging (SWI) and T2*).

In addition to appropriate MRI studies, it is important for physicians to consider the presence of SHS. Most physicians usually do not suspect SHS; therefore, establishment of clinical guidelines for the diagnosis of SHS is crucial for patients with SHS. The types of SHS and their treatment remain controversial because the number of reports is limited. Although two reports analyzed a relatively large number of cases [3,4], most other studies have dealt with only one or a few cases.

In 2015, the Ministry of Health, Labour and Welfare of Japan added SHS as an "intractable disease" for which patients are eligible to receive financial support from the government for treatment. To confirm the diagnosis of SHS, diagnostic criteria of SHS were established. We conducted a nationwide survey, to clarify the epidemiological and clinical features of SHS in Japan. Based on the survey results, we have revealed that SHS is not a rare clinical condition in Japan and must be considered as a possible diagnosis in patients with characteristic clinical presentations.

2. Methods

2.1. Survey instrument

The survey instrument used in the present study was a questionnaire in Japanese language, which consisted of six questions regarding cases of SHS from 2011 to 2016 and the methods of diagnosis and treatment at each institute surveyed. The questionnaire comprised multiple choice, yes or no, and fill-in-the-blank questions; some items included free-text comments (Table 1). The diagnosis and classification of each case were carried out using the criteria for SHS published in 2015 for the subsidy application under the Act on Medical Care for Patients with Intractable/Rare Diseases of Japan (Table 2). The classification of SHS sometimes varies in previous reports and may create confuse physicians to reach proper clinical diagnosis of SHS. In the criteria, the classic form and localized form of SHS are diagnosed based on the distribution of iron deposits recognized by MRI. Although the etiology of both types of SHS may be different, extensive analysis must be carried out to obtain the proper etiology of SHS.

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Table 1
Multidisciplinary questionnaire used in this survey.

Multidisciplinary questionnaire used in this survey
【Question 1】
1 Name of respondent
2 Name of the institute in which you work
3 Specialty of respondent
☐ Neurology ☐ Neurosurgery ☐ Otolaryngology ☐ Other
【Question 2】
Does your institute have experience with patients who have superficial hemosiderosis (SHS) according to the diagnostic criteria (provided)?
☐ Yes (continue below)
☐ No (The questionnaire is now completed)
☐ N/A, the institute has no MRI
【Question 3】
Number of patients with SHS
Classical type ___ patients
Localized type ___ patients
Atypical type ___ patients
【Question 4】
Details of each patient with SHS
Type ☐ Classical ☐ Localized ☐ Atypical
Age at onset
Sex
Initial symptom
Other symptoms
Modified Rankin Scale (mRS) score
Eating Function scale score
Respiratory Status scale score
Known etiology of SHS (yes/no)
* If yes, etiology of SHS (please select from among the following)
☐ cerebral aneurysm or cerebral arteriovenous fistula
☐ amyloid angiopathy
☐ tumor of the brain or spinal cord
☐ trauma
☐ cerebrospinal fluid hypovolemia
☐ cystic disease or dural abnormality in the spinal canal
☐ other
Findings of cerebrospinal fluid
cell count
red cell count
total protein
glucose
iron
ferritin
Recipient of grant approval under the Act on Medical Care for Patients with Intractable/Rare Diseases by the Ministry of Health, Labour and Welfare of Japan (yes/no)
【Question 5】
If you know, please indicate the method of diagnosis for SHS at your institute:
1 Magnetic field strength of MRI used for diagnosis (T)
2 Sequence of brain MRI used for diagnosis (T2, T2*, SWI)
3 Do you use brain magnetic resonance angiography (MRA) to detect the cause of SHS?
4 Do you use another brain MRI sequence, including enhanced MRI, to detect the cause of SHS? (yes/no)
* If yes, please provide details here ( )
【Question 6】
Do you treat any patients with SHS? (yes/no)
* If yes, please provide details of treatment ( )

2.2. Survey distribution

A list of medical institutes, to which we sent questionnaires in this research, was provided by the Japanese Society of Neurology (JSN). These institutes have been approved by the JSN as teaching hospitals for board-certified neurologists. We sent questionnaires to 792 institutes via postal mail.

In this report, the data collected in the surveys included patient age, sex, symptoms, etiology, classification, modified Rankin Scale (mRS) score, Eating Function scale score, Respiratory Status scale score, and cerebrospinal fluid (CSF) test results; these data represented the number of patients. Data such as neuroimaging and treatment represented the number of institutes.

Table 2
Criteria for the diagnosis of superficial hemosiderosis (SHS) as defined by the Japanese Ministry of Health, Labor and Welfare (2015).

Definition: Superficial hemosiderosis (SHS) is a disease characterized by hemosiderin deposition on the surface of the brain, which causes various neurological symptoms. There are three SHS entities: "classical" SHS shows diffuse bilateral deposition of iron (hemosiderin) across the central nervous system, mainly in the cranial cerebellum, brainstem, and posterior cranial fossa; "localized" type SHS effects the brain locally, for instance, the side frontal lobe and so on; "atypical" type SHS is described below. "Classical" type SHS is usually referred to as SHS in previous studies.
For diagnosis of classical type SHS, one of four clinical symptoms and at least one diagnostic imaging result must be confirmed, as below.
Clinical symptoms of "classical" type SHS
1. Sensorineural deafness
2. Cerebellar ataxia
3. Myelopathy (gait disturbance, dysuria, numbness, and so on)
4. Cognitive impairment
Most cases of SHS are detected according to sensorineural deafness or cerebellar ataxia as the initial symptom. Cases without these symptoms or with only other symptoms are classified as "atypical" type SHS. The characteristic symptoms of "localized" SHS are unclear to date.
Imaging tests
MRI is essential for the clinical diagnosis of SHS, with patients diagnosed using MRI findings.
1. In T2-weighted imaging, T2*-weighted images are typically diffuse, and symmetrical low-intensity signals bordering the surface of the brain and spinal cord are noted. These findings are predominant in the posterior cranial fossa, such as the cerebellum and brainstem. Involvement of the cranial nerves and spinal cord and lesions associated with localized atrophy are common.
2. As for the etiology of SHS, cerebral arterial aneurysm, cerebral arteriovenous fistula, amyloid angiopathy, brain and spinal cord tumor, trauma, cerebrospinal fluid depletion, cystic disease in the spinal canal, and dural anomaly have been reported. Therefore, appropriate MRI sequences should be included for SHS diagnosis.
3. In some cases, distinction must be made between localized hemosiderin deposition caused by the disease (as in no. 2), such as only on one side of the frontal lobe, and symmetric diffuse hemosiderin deposition (as in no. 1).
Drawbacks of MRI
1. To detect hemosiderin deposition, T2- and T2*-weighted images are necessary. Susceptibility-weighted images (SWI) can replace T2* imaging.
2. For confirmation of underlying disease or lesions, contrast-enhanced T1 imaging of the head, magnetic resonance angiography (MRA), T2 and contrast-enhanced T1 imaging emphasizing images of the spinal cord with fat suppression, MR or computed tomography (CT) myelography, or spinal angiogram could be important. In addition, evaluation for spinal vascular lesions and dural anomaly might be appropriate in some cases. Congenital and acquired abnormalities of the dura mater inside and around the spinal canal and various conditions accompanied by SHS have been reported. Abnormal localized dilation, in or connected with the subarachnoid space, is another typical finding.
Cerebrospinal fluid analysis
Increases in red blood cell count, total protein, iron, and ferritin have been reported; however, the role of these needs further examination.

Table 3
Patients with SHS, classified according to type.

Type	Male	%	Female	%	Total	%
c-SHS	49	65.3	32	66.7	81	65.9
l-SHS	20	26.7	9	18.8	29	23.6
a-SHS	6	8.0	7	14.6	13	10.6
Total	75	100.0	48	100.0	123[a]	100.0

Abbreviations: SHS, superficial hemosiderosis; c-SHS, classical type SHS; l-SHS, localized type SHS; a-SHS, atypical type SHS.
[a] Five patients with l-SHS were excluded owing to missing information.

3. Results

3.1. Survey results

We received completed questionnaires from 287 institutes (36.2%), among which patients with SHS were seen at 55 institutes, including 27 university hospitals.

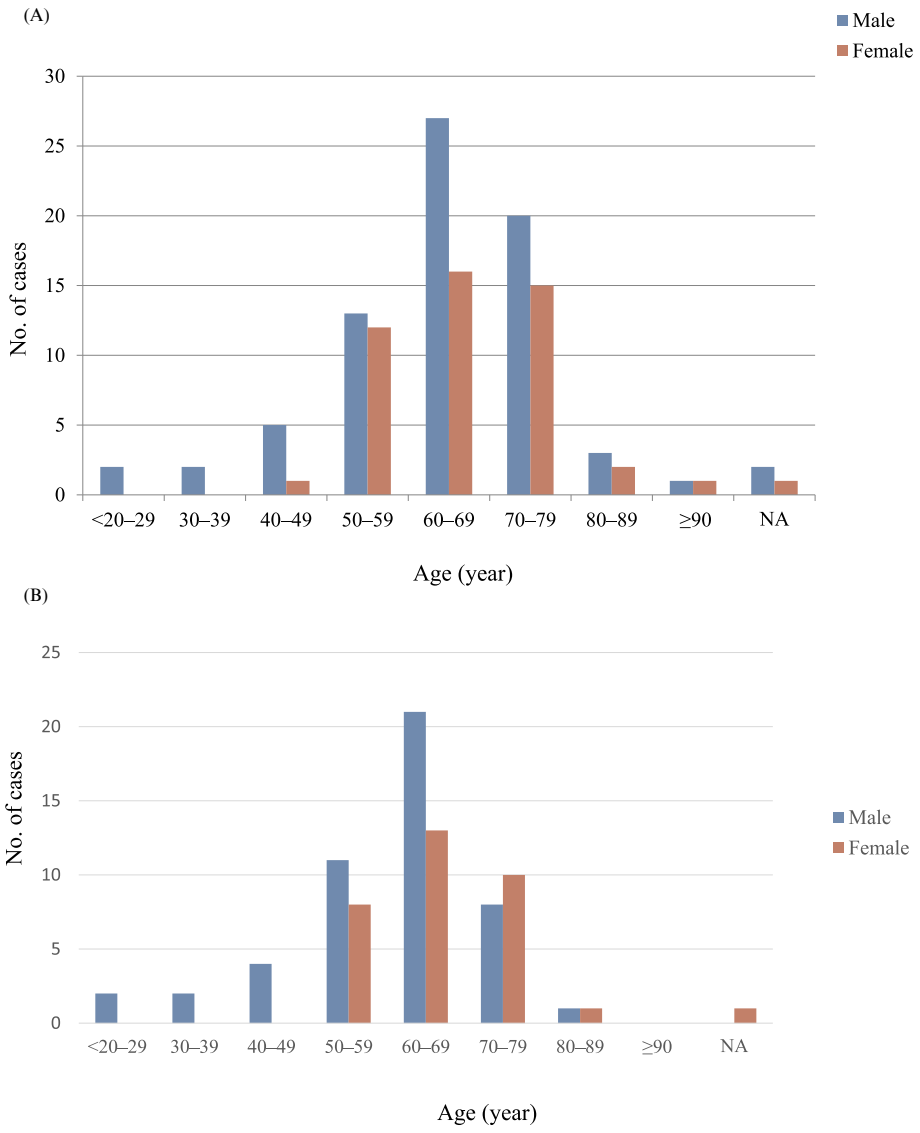

Fig. 1. Age and sex distributions in patients with SHS, for the total (a) and c-SHS (b). The most affected age group was 60–69 years in both sexes.
NA, not available.

3.2. Distributions by age and sex

Based on the criteria of the Japanese Ministry of Health, Labor and Welfare, 128 patients were diagnosed with SHS. These patients were classified as having "classical" type (c-SHS; $n = 81$, 65.9%), "localized" type (l-SHS; $n = 29$, 23.6%), or "atypical" type (a-SHS; $n = 13$, 10.6%); five patients with l-SHS were excluded owing to missing detailed information (Table 3). Six patients lacked information of sex and age. There were 75 male patients and 47 women, and the sex ratio was 1.6. The mean (SD) age was 63.5 (12.4) years in men and 66.4 (10.3) in

Table 4
Etiology according to each SHS entity in Japan.

Etiology	c-SHS			l-SHS			a-SHS		
	n (%)			n (%)			n (%)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Cerebral aneurysm or cerebral arteriovenous fistula	2 (5.9)	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Amyloid angiopathy	2 (5.9)	1 (4.5)	3 (5.4)	13 (86.7)	1 (100.0)	14 (87.5)	1 (25.0)	0 (0.0)	1 (14.3)
Tumor of the brain or spinal cord	2 (5.9)	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Trauma	5 (14.7)	0 (0.0)	5 (8.9)	1 (6.7)	0 (0.0)	1 (6.3)	2 (50.0)	0 (0.0)	2 (28.6)
Cerebrospinal fluid hypovolemia	2 (5.9)	2 (9.1)	4 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	2 (66.7)	3 (14.3)
Cystic disease or dural abnormality in the spinal canal	16 (47.1)	12 (54.5)	28 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	3 (42.9)
Other disease	5 (14.7)	7 (31.8)	12 (21.4)	1 (6.7)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Total	34 (100)	22 (100)	56 (100)	15 (100)	1 (100)	16 (100)	4 (100)	3 (100)	7 (100)

Abbreviations: SHS, superficial hemosiderosis; c-SHS, classical type SHS; l-SHS, localized type SHS; a-SHS, atypical type SHS.

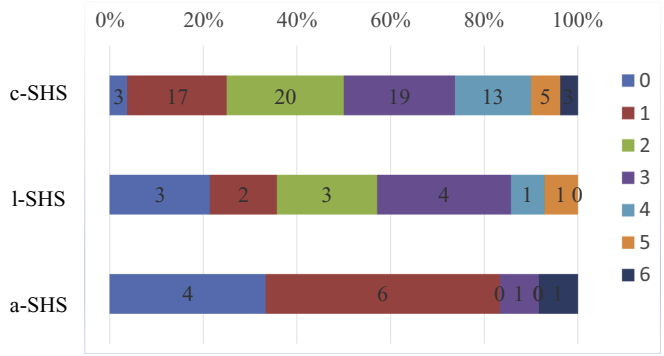

Fig. 2. Distribution of mRS scores for the three types of SHS.
SHS, superficial hemosiderosis; c-SHS, classical type SHS; l-SHS, localized type SHS; a-SHS, atypical type SHS.

women. Fig. 1 shows the distribution of all patients by age and sex. The mean (SD) age of patients with c-SHS was 60.0 (12.1) in men and 65.6 (9.0) in women. Among all patients with SHS, the largest age group was 60–69 years for both sexes (Fig. 1a). The age distribution among patients with c-SHS was similar to that of the total patients (Fig. 1b).

3.3. Etiology

The causes of SHS were reported for 77 patients (63%): 56 with c-SHS, 16 with l-SHS, and 7 with a-SHS (Table 4). Cystic disease and/or dural abnormality (so called duropathy of the spinal canal), trauma, and intracranial hypovolemia were the main causes of c-SHS. In men, duropathy was the leading cause (47.1%), followed by trauma (14.7%). In women, duropathy was also the leading cause of c-SHS, and the second leading cause was intracranial hypovolemia (9.1%). Duropathy in c-SHS was frequently observed in patients aged 60–69 years. In l-SHS, most cases were associated with cerebral amyloid angiopathy (Table 4). Duropathy could accompany with intracranial hypovolemia, however theoretically there might be continuous bleeding by duropathy without intracranial hypovolemia as main etiology of SHS. Thus, these two conditions were confirmed independently in the questionnaire.

3.4. Initial symptoms

Based on the results of our survey, most patients showed one of the four characteristic symptoms of c-SHS laid out in diagnostic criteria. The most common initial symptom was cerebellar ataxia (n = 36, 44.4%) followed by sensorineural deafness (n = 44.4, 42.0%); these symptoms were both more frequent than myelopathy (n = 6, 7.4%) and cognitive dysfunction (n = 8, 9.9%).

3.5. mRS

The distribution of mRS scores, with scores ranging from 0 to 6 [5] is shown in Fig. 2. More than 50% of individuals with c-SHS and l-SHS were in a condition of dependence.

3.6. Eating function and respiratory status

In Japan, the eating function and respiratory condition of patients with most “intractable disorders” is assessed using the following scales. Eating function: 0, no symptoms at all; 1, sometimes showing symptoms of aspiration or clumsy movements but no hindrance of social and daily life.; 2, needing some consideration of the form of foods or implements used for meals.; 3, needing some assistance with eating meals or nutritional intake; 4, need for sputum suction equipment or intermittent ventilation; 5, need for tracheotomy or continuous ventilation equipment.

Table 5
Respiratory status and function, according to type of SHS.

Respiratory status scale score	c-SHS (n)	l-SHS (n)	a-SHS (n)
0	76	13	11
1	4	1	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	1
N/A	1	20	1
Eating function scale score	c-SHS (n)	l-SHS (n)	a-SHS (n)
0	50	11	10
1	19	0	1
2	4	0	0
3	5	3	0
4	0	0	0
5	2	0	1
N/A	1	20	1

Abbreviations: SHS, superficial hemosiderosis; c-SHS, classical type SHS; l-SHS, localized type SHS; a-SHS, atypical type SHS; N/A, not applicable.

Respiratory status: 0, no symptoms at all; 1, declining lung capacity, but no hindrance of social and daily life.; 2, symptoms such as mild shortness of breath owing to respiratory disorders; 3, respiratory symptoms that disturb sleep, or shortness of breath conducting activities of daily living, such as getting dressed; 4, needing parenteral nutrition support (i.e., feeding via tube or central venous catheter); 5, complete dependence on parenteral nutrition. These conditions, summarized in Table 5, were not very severe among all SHS individuals.

3.7. Cerebrospinal fluid (CSF) analysis

Patients with c-SHS (n = 52, 64%), l-SHS (n = 7, 21%), and a-SHS (n = 5, 38%) underwent CSF testing. The average and standard deviation of outcomes are shown in Table 6. The level of total protein and number of cells were higher in c-SHS, although there was no statistical difference owing to the small number of cases.

3.8. Neuroimaging

The magnetic field strength and sequence of MRI in the diagnosis of SHS at each institute are shown in Fig. 3. Both 1.5 T and 3 T MRI images were used in the clinical diagnosis. Various combinations of MRI sequences were selected at many institutes. In particular, susceptibility-weighted imaging (SWI) or T2*-weighted imaging, both sensitive sequences to detect hemosiderin, were carried out in all cases. No institute makes diagnosis with only T2WI on 1.5 T. In addition to brain MRI, magnetic resonance angiography (MRA) was also performed at 45 institutes (81%), enhanced MRI was conducted at 24 (30%), and spinal MRI was used at 38 (69%) institutes.

3.9. Treatment

Treatment for SHS was provided at 31 (56.4%) institutes (Fig. 4). In some instances, the same patient received several treatments. Hemostatic drugs were used at 13 institutes. In nine surgical procedures, dural repair, ventricular shunting, and cochlear implantation were performed.

3.10. Application for specific disease treatment to the Japanese Ministry of Health, Labor and Welfare

Applications for medical expense subsidies, based on the Act on Medical Care for Patients with Intractable Rare Diseases of Japan, were filed in 41% of patients with SHS at the time of this study.

Table 6
Average results of cerebrospinal fluid testing.

	Number of cells			Red cells	Total protein	Glucose	Iron	Ferritin
	Total	Poly	Mono					
c-SHS (n = 52)	13.7	11.2	2.7	8848	80.7	63	30.9	201
l-SHS (n = 7)	3.1	2.3	0.7	0	45.7	67	N/A	N/A
a-SHS (n = 5)	2.6	2.2	0.4	221	52.8	54	6.3	41

Abbreviations: Poly, polynuclear cells; Mono, mononuclear cells; c-SHS, classical type SHS; l-SHS, localized type SHS; a-SHS, atypical type SHS; N/A, not applicable.

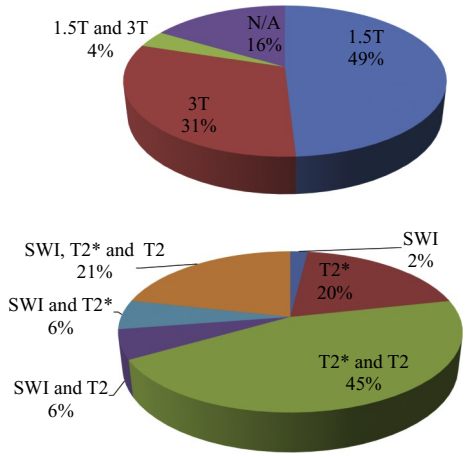

Fig. 3. Distribution of the magnetic field strength and MRI sequence in the diagnosis of SHS at each institute.
SWI, susceptibility-weighted imaging; NA, not available.

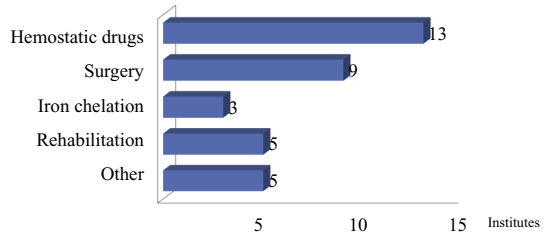

Fig. 4. Details of treatment for superficial hemosiderosis at each institute.

4. Discussion

As far as we know, ours is the first nationwide survey to clarify the clinical features, etiology, and various other conditions in SHS. Although we sent questionnaires to only neurology institutes, we believe that the results may help to deepen understanding of SHS among many physicians. Of particular interest, we found that there were more SHS cases than expected, although questionnaires were only sent to neurology institutes and there was a less than 40% response rate. Because various clinical symptoms may be present in SHS, neurosurgeons [6–8] and otorhinolaryngologists may also encounter patients with SHS [9,10]. Therefore, it is possible that there are a large number of cases of SHS that were not properly diagnosed. In addition, patients might be diagnosed with different conditions including spinocerebellar ataxia [11] and spinal canal stenosis. We should be aware of the possibility of SHS, especially in the case of slowly progressive ataxia, myelopathy, and hearing impairment [1]

In this study, there were more men than women with SHS. This observation is in agreement with previous studies describing the sex of patients with SHS [1,3,4]. In this study, cerebral aneurysm, cerebral arteriovenous fistula, tumor, and trauma were not seen in female patients with SHS. According to a large epidemiological study in Japan [12], cerebral aneurysm occurs twice as frequently in women as in men in Japan. Therefore, it is difficult to simply compare the sex ratio of disorders associated with subarachnoid bleeding and that of SHS.

The clinical diagnosis of SHS is challenging because SHS may show similar clinical features to spinocerebellar ataxia [13]. Undoubtedly, using MRI with high magnetic field is crucial to detect hemosiderin [14,15]. We strongly recommend 1.5 T or 3 T MRI including T2* or SWI imaging for individuals with cerebellar ataxia or myelopathy, to identify SHS.

In nearly half of cases undergoing CSF testing, there was evidence of active bleeding in patients with c-SHS. In some case reports, surgical procedures improve continuous subarachnoid bleeding [7,16]. In contrast, a few patients with c-SHS had cell counts, including red blood cells, in CSF that were within the normal range. Because there may be intermittent subarachnoid bleeding in some cases, repeated CSF examination may be necessary in cases of SHS [1].

A number of patients were treated with hemostatic drugs. However, the effectiveness of these medications is unclear. In addition, three institutes treated their patients with iron chelators. There is recent preliminary evidence of the safety and tolerability as well as effectiveness and improvement in neuroimaging of deferiprone, an iron-chelating drug that crosses the blood–brain barrier [17–19]. There are no data for long-term patient prognosis. Further analysis is necessary to confirm the effects of deferiprone. It must be emphasized that it is difficult for other iron chelators to cross the blood–brain barrier.

Because dural abnormality of the spinal cord (duropathy) is considered an important cause of subarachnoid bleeding in SHS, the possibility of dural repair must be evaluated in all patients [20]. Although there have been no large randomized studies in this regard, surgical treatment of causal structural anomalies might be effective in ameliorating clinical symptoms [16]. If other causes of subarachnoid bleeding are present, the possibility of surgical treatment must be considered.

Previous reports have stated that progression to a dependent state may occur over decades in up to one-fourth of patients with SHS [1]. In the present study, patients with SHS appeared to maintain their activities of daily living, based on scores of the mRS and Eating Function and Respiratory scales. Therefore, it is important to halt the clinical worsening of SHS as early as possible. Future analysis and systematic trials of treatments may be warranted, to establish the optimal management of SHS.

The limitations of the present study are as follows. 1) Because this study was conducted in Japan, we cannot generalize the results to populations in other countries. 2) We were unable to access precise clinical information and neuroimaging results. 3) Owing to the small number of institutes that completed the survey, the data were insufficient to clarify the nature and basic characteristics of SHS. 4) The definitions of the SHS subtypes have not been standardized. For example, c-SHS in our criteria is called “infratentorial superficial siderosis” (iSS) in other studies [4]. Therefore, unified criteria and definitions of SHS are needed in further research.

5. Conclusions

In conclusion, we report the results of the first survey of SHS in

Japan. We consider that SHS is not a rare disorder and that there are more cases of SHS than previously thought. We also believe that the findings of this survey and our criteria of SHS will help clinicians to understand the necessity of adequate imaging in the differential diagnosis of individuals who have sensorineural hearing loss, ataxia, and myelopathy.

Financial disclosure

Masayuki Ohira - None.
Masaki Takao - None.

Ethics statement

This study was approved by the Saitama Medical University International Medical Center Institutional Review Board (No. 16–219).

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Declaration of Competing Interest

None.

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