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ORIGINAL RESEARCH

Recognition and Practice of Hypopituitarism After Traumatic Brain Injury and Subarachnoid Hemorrhage in Japan: A Survey

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ABSTRACT

Introduction: Individuals with traumatic brain injury (TBI) or subarachnoid hemorrhage (SAH) are at a high risk of hypopituitarism, and should benefit from early diagnosis and management. However, data on awareness, attitudes, and practices of physicians treating hypopituitarism post-TBI/SAH are limited. The objectives of this study were to gain an understanding of the awareness of Japanese neurosurgeons and endocrinologists towards hypopituitarism post-TBI/SAH and the need for pituitary function assessments in these patients; and to assess the practices and perspectives of these specialists on screening patients with this condition.

Methods: An observational, cross-sectional study was performed that included a Web-based survey of practicing neurosurgeons managing ≥ 1 new patients with TBI/SAH per year or endocrinologists with ≥ 1 new patients per year with a history of TBI/SAH.

Results: Of the 316 respondents (201 neurosurgeons [male, 95.5%]; 115 endocrinologists [male, 77.4%]), 75.6% of neurosurgeons and 81.7% of endocrinologists were aware of the probable occurrence of hypopituitarism post-TBI/SAH, and 79% neurosurgeons and 93.8% endocrinologists considered pituitary function impairment after TBI/SAH to be either very important or important. Hypopituitarism after TBI/SAH was recognized as an important concern by both neurosurgeons (79%) and endocrinologists (93.8%). Although many respondents agreed that such patients remain undiagnosed and untreated, pituitary function assessment post-TBI/SAH has only been performed to a limited extent. The awareness that post-TBI/SAH hypopituitarism is often transient and can progress over several weeks or months was lower in neurosurgeons (46.8%) than in endocrinologists (66.1%).

Conclusions: The level of awareness of hypopituitarism post-TBI/SAH was lower among Japanese neurosurgeons than among endocrinologists. Educational programs and detailed guidance for the diagnosis and treatment of hypopituitarism post-TBI/SAH are warranted.

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Key Summary Points

Why carry out this study?

Individuals with traumatic brain injury (TBI) or subarachnoid hemorrhage (SAH) are at a high risk of hypopituitarism and should, therefore, benefit from early diagnosis and management. However, data on awareness, attitudes, and practices of treating physicians are limited.

The objectives of this study were to gain an understanding of the current state of awareness of Japanese neurosurgeons and endocrinologists towards hypopituitarism post-TBI/SAH and the need for pituitary function assessments in these patients as well as to assess the practices and perspectives of these specialists on screening patients with this condition.

What was learned from the study?

Hypopituitarism after TBI/SAH was recognized as an important concern by both neurosurgeons (79%) and endocrinologists (93.8%). The awareness that post-TBI/SAH hypopituitarism is often transient and can progress over several weeks or months was lower in neurosurgeons (46.8%) than in endocrinologists (66.1%).

The level of awareness of hypopituitarism post-TBI/SAH was lower among Japanese neurosurgeons than among endocrinologists. Educational programs and detailed guidance for the diagnosis and treatment of hypopituitarism post-TBI/SAH are warranted.

INTRODUCTION

Traumatic brain injury (TBI), often caused by falls and motor vehicle road accidents [1], is a growing global public health concern due to associated high mortality and morbidity [2]. TBI is recognized as a main cause of disability and death among young adults [3]. The associated morbidities can be temporary or permanent, and the disabilities can vary from only physical disabilities to impairments in cognitive, behavioral, and psychosocial functioning [4]. Globally, in 2016, there were 27.08 million incident cases of TBI, with an age-standardized incidence rate of 369 per 100,000 population, while TBI prevalence was 55.50 million and the prevalence rate was 759 per 100,000 population [1]. In Japan, the 2016 estimates report an incidence rate of 263 per 100,000 population and a prevalence rate of 474 per 100,000 population, with a decreasing trend in both [1].

Subarachnoid hemorrhage (SAH) or bleeding in the subarachnoid space was responsible for 8.9% of all incident strokes globally in 2017 [5]. Compared with other countries, the incidence of SAH was highest in Japan, with 47.2 cases per 100,000 population per year, resulting in 4.7 deaths per 100,000 population and 172.1 disability-adjusted life years per 100,000 population [5]. In another recent register-based SAH study in Japan, Ikawa et al. concluded that despite the recent decrease in incidence rates of SAH, Japan has a higher SAH incidence rate than other countries [6].

Because TBI/SAH involves underlying brain damage, individuals with TBI/SAH are at a high risk of hypopituitarism, which may manifest as partial or total hypopituitarism due to deficiency in the synthesis of one, many, or all of the hormones produced by the pituitary [7]. Deficiencies of growth hormone (GH), adrenocorticotropic hormone (ACTH), or gonadotropic hormones are commonly reported in individuals with TBI/SAH [8, 9]. However, the exact mechanism and specific risk factors of hypopituitarism post-TBI/SAH remain unclear [10]. Post-traumatic hypopituitarism (PTHP), although known about for a century, was previously believed to be uncommon, with only a

few cases reported occasionally [8]. Current estimates suggest that 15–90% of the patients with TBI/SAH develop hypopituitarism, although in some cases it may remain unrecognized owing to its masking by effects of the brain injury, unawareness of treating physicians, and endocrine assessment being deprioritized in this patient population [8–11]. Schneider et al. used conservative statistics from the USA, Europe, and Australia and estimated that the annual incidence of hypopituitarism attributable to TBI/SAH was 31 cases per 100,000 population [12]. In general, both mild and moderate-to-severe TBI/SAH can result in hypopituitarism, which may remain undiagnosed and untreated and progress slowly with non-specific symptoms [8, 10].

Early diagnosis of hypopituitarism after TBI/SAH is important as hypopituitarism can hinder healing and rehabilitation and may lead to substantial morbidity in these patients. The approach to diagnosing hypopituitarism after TBI/SAH is similar to that to diagnosing classical hypopituitarism resulting from hypothalamic-pituitary dysfunction. Given the heterogeneous pattern of hormone insufficiency post-TBI/SAH hypopituitarism, each pituitary hormone needs to be assessed separately in patients with a suspicion of this condition [13]. Thus, it is imperative that endocrinologists are involved in a timely manner in diagnosing hypopituitarism in patients with TBI/SAH and in treating hypopituitarism in acute, subacute, or chronic phases of TBI/SAH.

However, non-referrals or delayed referrals of post-TBI/SAH patients to endocrinologists by treating physicians appear to be a major obstacle to improving outcomes. Treating physicians (e.g., neurosurgeons) are often unaware of the need for pituitary evaluation in both children and adults and believe that mild TBI is benign [14]. Furthermore, a visible gap exists between the awareness levels and the actual practice patterns pertaining to PTHP among neurosurgeons, as seen in a UK-based study of surveillance practices pertaining to PTHP [15]. In this survey, despite most (86.7%) of the 45 neurosurgeons included in that study acknowledging that PTHP was a problem, only 25% reported regularly screening for PTHP, with the rate of routine pituitary function tests for patients with TBI relatively low. Overall, the clinical parameters thought to prompt screening and the interval to screening were highly variable [15]. Similar data from other countries, including Japan, are unavailable.

The aim of this study was to gain an understanding of the current state of awareness of Japanese neurosurgeons and endocrinologists pertaining to: (1) the occurrence of hypopituitarism after TBI/SAH and (2) the need for pituitary function assessments in these patients. We also assessed the current practices and perspectives of Japanese neurosurgeons and endocrinologists relevant for screening these patients for undiagnosed post-TBI/SAH hypopituitarism.

METHODS

Study Design

This was an observational, cross-sectional study conducted using a Web-based survey in December 2021.

Participants

Participants were recruited from a registered panel of Japanese physicians that is maintained by Plamed Inc., a wholly-owned subsidiary of INTAGE Healthcare (Tokyo, Japan). Plamed maintains a panel of approximately 81,000 physicians practicing nationwide across Japan, representing about 27% of physicians in Japan, with good representation in terms of regions, specialties, and facility types. The panel includes about 1500 neurosurgeons and 700 endocrinologists.

The inclusion criteria were: (1) licensed and practicing physicians in Japan registered in the Plamed panel; (2) neurosurgeons with at least one new patient of TBI and/or SAH (TBI/SAH) per year or endocrinologists with at least one new patient with a history of TBI/SAH per year; the endocrinologists or neurosurgeons had to be personally involved in the treatment of TBI

and/or SAH patients; and (3) providing informed consent for participating in the study.

The physicians were screened for inclusion criteria using a screening questionnaire and those who qualified for inclusion were invited to complete an online survey.

Survey Questionnaire

The online survey (Electronic Supplementary Material [ESM] Table S1), which required 10–15 min to complete, contained about 40 questions in a selective or numerical response format and covered the following items: (1) physician demographics; (2) number of TBI/SAH patients per year; (3) awareness and importance of hypopituitarism; (4) awareness of information surrounding hypopituitarism; and (5) status regarding the implementation of pituitary function tests.

The questionnaire was drafted by the Medical Affairs Department experts at Novo Nordisk Pharma Ltd. (Tokyo, Japan) after a thorough literature survey, under the supervision of an external endocrinologist and neurosurgeon (the authors of this paper). The questionnaire was designed to target the study objectives and uncover the relevant real-world descriptive data.

A request for participation was distributed to the physicians with the title "A survey of physicians on symptoms after TBI/SAH" without mentioning hypopituitarism to avoid any form of bias in the responses. The responses were recorded into an electronic database. After completing the survey, participants were paid an honorarium based on fair market value for their participation. The survey was double-blinded to avoid any sponsorship-induced response bias. All participants were anonymized and given a unique participant ID.

Statistical Analyses

The target sample size was at least 300, including 200 neurosurgeons and 100 endocrinologists. Statistical analyses were generally descriptive. Categorical variables were reported using frequency and percentages, and continuous variables were reported using mean and standard deviation (SD). For categorical variables of interest, Chi-square (χ^2) tests were used to study differences in the groups at a significance level of $p < 0.05$. Specifically, the statistical differences were assessed for the following single-answer questions: (1) How clinically significant a problem do you consider the fact that pituitary function may be impaired after TBI/SAH? (2) Do you know that initial hypopituitarism after TBI/SAH is often transient and can progress over several weeks or months? (3) Do you know the criteria for insurance coverage of growth hormone therapy? If necessary, a residual analysis was performed in addition to the Chi-square test to examine significant differences in the selection rates of specific alternatives. Statistical analyses were performed using the R software (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria).

Ethical Considerations

The study was conducted in accordance with the protocol, the Declaration of Helsinki [16], and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [17] Good Clinical Practice Guidelines (ICH), and other applicable laws and regulations of Japan, as appropriate. All participants provided informed consent for participation and also for publication of aggregate anonymized data in scientific conferences and journals. The study was approved by the Ethics Committee (Committee number 16000061) of Saga Memorial Hospital (approval date: 2 November 2021).

RESULTS

Physician Demographics

This survey was completed by 316 respondents (201 neurosurgeons; 115 endocrinologists). Among the neurosurgeons and endocrinologists, 95.5% and 77.4% were male, respectively, and 78.6% and 86.1% were between 30

and < 60 years old. The majority (87.1%) of neurosurgeons identified themselves as general neurosurgeons, while 90.4% of endocrinologists identified themselves as specialist in diabetes mellitus and 80.9% identified themselves as specialist in endocrine disorders (treating disorders of the hypophysis, thyroid, parathyroid, and paranephric) (Table 1). Information on the specialty certification, type of facility, and number of beds in facility associated with each participating neurosurgeon and endocrinologist is shown in Table 1.

Number of TBI/SAH Patients Per Year

The mean (SD) number of cases of TBI managed by each neurosurgeon and endocrinologist personally each year were 49.7 (94.8) and 3.6 (4.6), respectively. The corresponding numbers for SAH were 12.3 (11.1) and 3.7 (7.9), respectively (Table 2).

Awareness and Importance of Hypopituitarism

A majority of the respondents (75.6% of neurosurgeons and 81.7% of endocrinologists) were aware that hypopituitarism may occur after TBI/SAH, whereas only 3.0% of neurosurgeons and 1.7% of endocrinologists were totally unaware. Most respondents considered pituitary function impairment after TBI/SAH to be either very important or important (79% for neurosurgeons and 93.8% for endocrinologists; significantly different at $p = 0.00054$) (Table 2). Around 37.8% of neurosurgeons and a majority of endocrinologists (77.4%) were of the opinion that routine pituitary function tests are needed to screen for hypopituitarism post-TBI/SAH, while 40.3% of neurosurgeons and 12.2% of endocrinologists responded that they do not know whether routine pituitary function tests are needed to screen for hypopituitarism post-TBI/SAH. Regarding the optimum time for pituitary function testing for screening hypopituitarism, 64.5% of neurosurgeons and 49.5% of endocrinologists responded that a pituitary function test is necessary within a week or month post-injury (TBI/SAH) (Table 2).

Table 1 Baseline information of the participating neurosurgeons and endocrinologists

Physician characteristics	Neurosurgeons, *n* (%)	Endocrinologists, *n* (%)
Sex		
Male	192 (95.5)	89 (77.4)
Female	9 (4.5)	26 (22.6)
Age, years		
20 to < 30	11 (5.5)	8 (7.0)
30 to < 40	50 (24.9)	49 (42.6)
40 to < 50	43 (21.4)	36 (31.3)
50 to < 60	65 (32.3)	14 (12.2)
60 to < 70	31 (15.4)	7 (6.1)
≥ 70	1 (0.5)	1 (0.9)
Specialty		
General neurosurgeon	175 (87.1)	
Head trauma	86 (42.8)	
Brain tumor	77 (38.3)	
Spinal cord/spine disease	21 (10.4)	
Headache	53 (26.4)	
Endocrine disorders (hypophysis, thyroid, parathyroid, paranephric)		93 (80.9)
Diabetes mellitus		104 (90.4)
Arteriosclerosis		40 (34.8)
Hypertension		49 (42.6)
Lipid disorders		60 (52.2)
Obesity		56 (48.7)
Metabolic disorders		51 (44.3)
Specialty certification		

Table 1 continued

Physician characteristics	Neurosurgeons, *n* (%)	Endocrinologists, *n* (%)
Japan Neurosurgical Society Specialist	183 (91.0)	
Japan Endocrine Society Specialist	8 (4.0)	
Specialists of other Societies	36 (17.9)	
Type of facility		
General hospital	103 (51.2)	46 (40.0)
University hospitals	43 (21.4)	27 (23.5)
National public hospitals	39 (19.4)	26 (22.6)
Clinics	16 (8.0)	16 (13.9)
Number of beds in facility		
0	13 (6.5)	15 (13.0)
1–19	3 (1.5)	1 (0.9)
20–99	10 (5.0)	10 (8.7)
100–199	29 (14.4)	8 (7.0)
200–499	77 (38.3)	38 (33.0)
500	69 (34.3)	43 (37.4)

Awareness of Information Surrounding Hypopituitarism

The awareness that initial hypopituitarism post-TBI/SAH may gradually progress was significantly lower among neurosurgeons than endocrinologists (46.8% vs. 66.1%; $p = 0.000918$) (Table 3). A total of 158 (78.6%) neurosurgeons and 107 (93.0%) endocrinologists believed that there were undiagnosed and untreated cases of hypopituitarism after TBI/SAH; of these, 48.7% neurosurgeons and 60.8% endocrinologists felt that the proportion of

Table 2 Responses by the participating neurosurgeons and endocrinologists on awareness and importance of hypopituitarism

Survey question	Neurosurgeons	Endocrinologists
How many new cases of (new patients with a history of) TBI and SAH do you see each year?, mean (SD)[a]		
TBI cases	49.7 (94.8)	3.6 (4.6)
SAH cases	12.3 (11.1)	3.7 (7.9)
Do you know that hypopituitarism may occur after TBI/SAH?[a]		
Aware	152 (75.6)	94 (81.7)
Partially aware	43 (21.4)	19 (16.5)
Unaware	6 (3.0)	2 (1.7)
How clinically significant a problem do you consider the fact that pituitary function may be impaired after TBI/SAH?[*,b]		
Very important or an important issue	154 (79.0)	106 (93.8)
Not an important issue	4 (2.1)	1 (0.9)
Don't know	3 (1.5)	0 (00)
Do you think routine pituitary function tests are needed to screen for hypopituitarism after TBI/SAH?[a]		
Yes	76 (37.8)	89 (77.4)
No	44 (21.9)	12 (10.4)
Don't know	81 (40.3)	14 (12.2)
At which time do you think pituitary function testing is necessary after injury to screen for hypopituitarism post-TBI/SAH?[c]		
Within 1 week	12 (15.8)	11 (12.4)
Within 1 month	37 (48.7)	33 (37.1)
2–6 months	16 (21.1)	31 (34.8)
After 6 months	2 (2.6)	2 (2.2)
When necessary	8 (10.5)	11 (12.4)

Table 2 continued

Survey question	Neurosurgeons	Endocrinologists
I don't know	1 (1.3)	1 (1.1)

Data are presented as *n* (%) unless specified otherwise
SAH subarachnoid hemorrhage, *SD* standard deviation, *TBI* traumatic brain injury
*$p = 0.00054$
[a]Number of respondents = 201 neurosurgeons and 115 endocrinologists
[b]Number of respondents = 195 neurosurgeons and 113 endocrinologists (physicians who responded as "I know" or "I've heard of it" regarding hypopituitarism after TBI/SAH)
[c]Number of respondents = 76 neurosurgeons and 89 endocrinologists (physicians who responded as "routine pituitary function tests are needed to screen for hypopituitarism after TBI/SAH")

untreated/undiagnosed patients with hypopituitarism post-TBI/SAH ranged from 10% to 50%. Awareness of the criteria for insurance coverage of GH therapy was also higher among endocrinologists than neurosurgeons (89.3% vs; 46.5%, respectively; $p < 0.00001$).

Status Regarding the Implementation of Pituitary Function Tests

Table 4 summarizes the responses provided by the neurosurgeons and endocrinologists regarding implementation of pituitary function tests. Among the respondents, 52.4% of neurosurgeons and 73.7% of endocrinologists responded that they had performed the pituitary function test on patients with TBI/SAH. Pituitary function testing post-TBI/SAH was performed in < 10% of patients by 70.7% of neurosurgeons and 47.6% of endocrinologists.

Regarding the assessment of pituitary function post-TBI/SAH injury, most physicians (92.9% of neurosurgeons and 91.7% of endocrinologists) responded that they decided whether to perform a pituitary function test based on the patient's symptoms of hypopituitarism, while fewer (34.3% of neurosurgeons and 22.6% of endocrinologists) performed a pituitary function test based on the severity of TBI/SAH.

Table 3 Responses by the participating neurosurgeons and endocrinologists on their awareness of information regarding hypopituitarism

Survey question	Neurosurgeons	Endocrinologists
Do you know that initial post-TBI/SAH hypopituitarism is often transient and can progress over several weeks or months?,[a]*		
Aware	94 (46.8)	76 (66.1)
Partially aware	75 (37.3)	33 (28.7)
Unaware	32 (15.9)	6 (5.2)
How many patients after TBI/SAH do you think are undiagnosed and untreated for hypopituitarism?[b]		
Less than 10%	61 (38.6)	29 (27.1)
10% to < 50%	77 (48.7)	65 (60.8)
50–80%	15 (9.5)	10 (9.3)
Nearly all cases	5 (3.2)	3 (2.8)
Do you know the criteria for insurance coverage of growth hormone therapy?†,[c]		
Yes	46 (46.5)	75 (89.3)
No	53 (53.5)	9 (10.7)

Data presented as *n* (%)
SAH subarachnoid hemorrhage, *TBI* traumatic brain injury
*$p = 0.000918$; in addition to the Chi-square test, a residuals analysis was conducted to determine if there was a significant difference in the percentage of "Aware" responses selected
†$p < 0.00001$
[a]Number of respondents = 201 neurosurgeons and 115 endocrinologists
[b]Number of respondents = 158 neurosurgeons and 107 endocrinologists (physicians who responded "I think that such patients exist to some extent" regarding the possibility that there are patients with undiagnosed and untreated hypopituitarism after TBI/SAH)
[c]Number of respondents = 99 neurosurgeons and 84 endocrinologists (physicians who have performed pituitary function testing for patients after TBI/SAH)

Table 4 Responses by the participating neurosurgeons and endocrinologists regarding the status of implementing pituitary function tests

Survey question	Neurosurgeons	Endocrinologists
Is pituitary function testing ever performed on patients after (with a history of) TBI/SAH?[a]		
Yes	99 (52.4)	84 (73.7)
No	83 (43.9)	26 (22.8)
I don't know	7 (3.7)	4 (3.5)
What percentage of your patients after (with a history of) TBI/SAH had pituitary function testing performed?[b]		
Less than 10%	70 (70.7)	40 (47.6)
10% to < 30%	23 (23.2)	26 (31.0)
30% to < 50%	2 (2.0)	9 (10.7)
50–80%	3 (3.0)	5 (6.0)
Almost all cases	1 (1.0)	4 (4.8)
How do you decide which patients to test?[b]		
Patients with some length of hospitalization	12 (12.1)	13 (15.5)
Based on the severity of TBI/SAH	34 (34.3)	19 (22.6)
Patients with symptoms of hypopituitarism	92 (92.9)	77 (91.7)
Other	0 (0.0)	2 (2.4)
How long, if usually, did you continue to perform pituitary function tests on patients post-TBI/SAH?[b]		
Less than 1 month	9 (9.1)	2 (2.4)
1 month to < 6 months	46 (46.5)	25 (29.8)
6 months to < 1 year	21 (21.2)	29 (34.5)
More than 1 year	7 (7.1)	23 (27.4)
I don't know	16 (16.2)	5 (6.0)
Which pituitary function tests have you performed?[b]		
GH	67 (67.7)	73 (86.9)
Pituitary-adrenal system	90 (90.9)	81 (96.4)
Pituitary-thyroid system	81 (81.8)	76 (90.5)
Pituitary-gonadal system	42 (42.4)	57 (67.9)
Prolactin	51 (51.5)	58 (69.0)
Other	13 (13.1)	3 (3.6)
What GH-related tests do you perform?[b]		
IGF-1	59 (59.6)	68 (81.0)
GH secretion stimulation test (insulin tolerance test)	23 (23.2)	28 (33.3)
GH secretion stimulation test (glucagon tolerance test)	14 (14.1)	16 (19.0)
GH secretion stimulation test (arginine tolerance test)	5 (5.1)	11 (13.1)
GH secretion stimulation test (GHRP-2 tolerance test)	13 (13.1)	60 (71.4)
I don't know	6 (6.1)	0 (0.0)
Not implemented	15 (15.2)	3 (3.6)
How many cases of hypopituitarism have you experienced as a result of the test?, mean (SD)[b]		
TBI cases	4.5 (5.59)	1.8 (2.02)
SAH cases	5.2 (8.58)	1.5 (1.94)
After TBI/SAH, what is your thought about identifying the sequela of TBI/SAH and hypopituitarism?[c]		

Table 4 continued

Survey question	Neurosurgeons	Endocrinologists
I feel that it is difficult to distinguish between them	145 (72.1)	89 (77.4)
I feel that it is possible to distinguish between them	18 (9.0)	17 (14.8)
I have never thought about it	37 (18.4)	9 (7.8)
Other	1 (0.5)	0 (0.0)

Data presented as *n* (%) unless specified otherwise
GH growth hormone, *GHRP-2* growth hormone-releasing peptide-2, *IGF-1* insulin-like growth factor-1, *SAH* subarachnoid hemorrhage, *SD* standard deviation, *TBI* traumatic brain injury
[a]Number of respondents = 189 neurosurgeons and 114 endocrinologists (physicians who have performed pituitary function tests [whether for TBI/SAH patients or not is not considered])
[b]Number of respondents = 99 neurosurgeons and 84 endocrinologists (physicians who have performed pituitary function testing for patients after TBI/SAH)
[c]Number of respondents = 201 neurosurgeons and 115 endocrinologists

Also, regarding the continuation period of pituitary testing, 55.6% of neurosurgeons and 32.2% of endocrinologists responded that they continued to perform the pituitary function test for < 6 months after TBI/SAH; 21.2% of neurosurgeons and 34.5% of endocrinologists responded that they continued performing the test for 6 months to 1 year.

Among the type of pituitary function tests performed by the physicians on patients with TBI/SAH injury, those for the pituitary–adrenal system, pituitary–thyroid system, and GH-related assessments predominated. Among GH-related tests, the two more common tests run for TBI/SAH were those for insulin-like growth factor-1 (IGF-1) (performed by 59.6% of neurosurgeons and 81% of endocrinologists) and GH secretion stimulation test–insulin tolerance (performed by 23.2% of neurosurgeons and 33.3% of endocrinologist). The GH secretion stimulation test–GH-releasing peptide (GHRP)-2 tolerance was another test commonly used by endocrinologists (71.4%).

The mean (SD) number of cases of TBI with hypopituitarism managed per neurosurgeon and endocrinologist at the time of the survey was 4.5 (5.59) and 1.8 (2.02), respectively; the corresponding numbers for SAH were 5.2 (8.58) and 1.5 (1.94), respectively. Regarding the identification of the sequela of TBI/SAH and hypopituitarism, most physicians (72.1% of neurosurgeons and 77.4% of endocrinologists) expressed that it is difficult to distinguish between them.

Details of the results based on additional questions included in the survey are presented in ESM Table S2.

DISCUSSION

Our online survey of awareness, attitude, and practices related to hypopituitarism after TBI/SAH among Japanese neurosurgeons and endocrinologists provides relevant data on current awareness levels and clinical practice patterns in Japan. Our results showed that 75.6% of neurosurgeons and 81.7% of endocrinologists were aware of the probable occurrence of hypopituitarism after TBI/SAH. Hypopituitarism after TBI/SAH was recognized as an important concern by both neurosurgeons (79%) and endocrinologists (93.8%). Overall, a higher proportion of endocrinologists compared to neurosurgeons were more knowledgeable and aware of the condition. Although many respondents agreed that such patients remain undiagnosed and untreated, pituitary function assessment post-TBI/SAH was performed only to a limited extent. The awareness that such hypopituitarism is often transient and can progress over several weeks or months was relatively low in neurosurgeons.

Patients, even those with mild TBI, may develop isolated or multiple pituitary hormone deficiencies. However, in post-TBI patients, as evidenced in this survey, pituitary function

might not be assessed or treated appropriately, leading to long-term consequences; this lack of assessment is probably due to a lack of awareness or initiative or both among the treating physicians. Also, some of the sequelae of TBI/SAH are similar to symptoms of hypopituitarism and the two conditions are considered difficult to distinguish [8, 13]. Taken together, these factors, among others, delay the screening of hypopituitarism post-TBI/SAH, at least partially. Furthermore, the level of awareness of the criteria for insurance coverage of GH therapy is very low (46.5%) in neurosurgeons (but higher in endocrinologists [89.3%]).

Adults with severe GH deficiency may be eligible for subsidized medical care under the system of designated intractable diseases in Japan. However, if the external causes of the disease onset are clear, the requirements for designation as an intractable disease are not met [18].

The diagnosis and criteria for severity of adult GH deficiency should also refer to the latest "Grant-in-Aid for Scientific Research on Ministry of Health, Labor and Welfare Guidance for diagnosis and treatment of adult growth hormone deficiency" classification of the disease [19].

Overall, the awareness level among treating physicians about pituitary dysfunction following TBI/SAH needs to be increased; in addition, a system needs to be developed that includes patient referral to endocrinologists for screening, regular assessment, and treatment of such patients in Japan. Physicians treating TBI/SAH need the following information and knowledge: (1) the details of symptoms of hypopituitarism following TBI/SAH; (2) how to distinguish between hypopituitarism and other sequelae after TBI/SAH; (3) the criteria for determining the need for pituitary function testing after TBI/SAH, and the appropriate timing and frequency of testing; and (4) the criteria for subsidies and insurance coverage. Thus, a multidisciplinary approach to increase awareness of the condition among neurologists, neurosurgeons, traumatologists, endocrinologists, and other care providers is warranted.

Globally, clinicians and scientific community are joining hands to develop consensus guidelines [14, 20]. In a recent review, Capizzi et al. summarized that the guidelines do not suggest routine monitoring of pituitary hormones in the acute phase in the absence of clinical suspicion, although in patients with disorders of consciousness, this assessment may be helpful [21]. The scientific community needs to urgently develop guidelines for the early identification and management of persistent PTHP across the severities of TBI [14].

In Japan, post-TBI/SAH hypopituitarism has not been actively discussed at length, and no detailed guidelines focusing on the screening and treatment of patients with potential hypopituitarism after TBI/SAH are available so far. Thus, it is possible that a certain proportion of such patients remain undiagnosed and untreated. It may therefore be necessary to discuss whether the information on how to manage post-TBI/SAH hypopituitarism (details of symptoms, necessity of testing, appropriate timing and frequency of testing, etc.) should be included in Japanese guidelines. Healthcare economic considerations should also be considered.

A number of limitations of this study must be acknowledged. First, the nature of the study (an online survey with multiple choice questions) may have led to recall bias and response bias, specifically a desirability bias. Second, the relatively limited sample size and inclusion of only neurosurgeons and endocrinologists in the study population may be considered as another limitation. Third, the severity of TBI/SAH was not considered in this survey; however, the assessment of the awareness of the physicians should not depend on the severity of TBI/SAH. Fourth, it must be noted that although the incidence of hypopituitarism after TBI/SAH is lower in patients with mild TBI, this patient population may also develop isolated or multiple pituitary hormone deficiencies. Fifth, although pituitary function may be affected by the treatment given in the acute phase of SAH and TBI, this factor was not accounted for in this study. Sixth, TBI and SAH are inherently different conditions, but in the present study they are discussed together for presentation purposes. Seventh, the neurosurgeon may be involved only in the acute management of TBI/

SAH and may not be involved in the long-term patient management. In some healthcare facilities, the emergency physician and the trauma surgeon may be involved in the management of TBI. Thus, there is a need to understand awareness of emergency physicians and trauma surgeons as well, which was not covered in the present study. Emergency physicians and trauma surgeons should also be educated regarding hypopituitarism after TBI/SAH. Eighth, it is possible that endocrinologists receive more referrals than neurosurgeons for suspected hypopituitarism, thus leading to the higher rate of pituitary function tests performed on these patients by endocrinologists. Lastly, the results obtained from this study may not be generalizable to other countries. Nevertheless, this survey provides a reference point for understanding the awareness, attitudes, and practices among Japanese neurosurgeons and endocrinologists from the aspect of not only TBI but also SAH.

CONCLUSIONS

Our study revealed the state of current knowledge and awareness level of post-TBI/SAH hypopituitarism among Japanese neurosurgeons and endocrinologists and the differences between them. Our results indicate scope for improving the awareness level among Japanese neurosurgeons and endocrinologists–especially in neurosurgeons–and the need to conduct further educational programs explaining hypopituitarism after TBI/SAH and factors associated with it. Lastly, more detailed guidance on the diagnosis and treatment of hypopituitarism after TBI/SAH should be developed as early as possible.

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Data Availability. There are no additional data. The dataset is available upon a reasonable request.

Declarations

Conflict of Interest. Shigeyuki Tahara has received payment for lectures and presentations from Novo Nordisk, Pfizer, and JCR Pharmaceuticals. Fumio Otsuka has received contracts from Novo Nordisk and grants from Pfizer and Eli Lilly, as well as payment for lectures from Novo Nordisk, Pfizer, Eli Lilly, and JCR Pharmaceuticals. Takaaki Endo is an employee and holds stock at Novo Nordisk Pharma Ltd. Medical writing support for this manuscript was funded by Novo Nordisk Pharma Ltd.

Ethical Approval. The study was conducted in accordance with the protocol, the Declaration of Helsinki and the International

Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines (ICH), and other applicable laws and regulations of Japan, as appropriate. The study was approved by the Ethics Committee of Saga Memorial Hospital.

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