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Clinical Study

Pituitary dysfunction after aneurysmal subarachnoid hemorrhage in Japanese patients

Yuko Goto [a,b], Satoru Oshino [b], Akio Nishino [c], Toshiyuki Fujinaka [d], Hajime Nakamura [b], Takamichi Yuguchi [e], Shintaro Mori [c], Toshiki Yoshimine [b], Youichi Saitoh [a,b,*]

[a] Department of Neuromodulation and Neurosurgery, Graduate School of Medicine, Osaka University, 2-2, Yamadaoka, Suita, Osaka Prefecture 565-0871, Japan
[b] Department of Neurosurgery, Graduate School of Medicine, Osaka University, Osaka Prefecture, Japan
[c] Department of Neurosurgery, Hanwa Memorial Hospital, Sumiyoshi Ward, Osaka, Osaka Prefecture, Japan
[d] Department of Neurosurgery, National Hospital Organization Osaka National Hospital, Chuo Ward, Osaka, Osaka Prefecture, Japan
[e] Yuguchi Neurosurgical and Spine Clinic, Tennoji Ward, Osaka, Osaka Prefecture, Japan

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ABSTRACT

To elucidate the pituitary function of Japanese patients after aneurysmal subarachnoid hemorrhage (aSAH) and implicative factors related to growth hormone deficiency (GHD) after aSAH. We evaluated basal pituitary hormone levels among 59 consecutive aSAH patients with a modified Rankin Scale (mRS) ⩽4 at 3 months after aSAH onset. Patients with low insulin-like growth factor 1 (IGF-1) SD score (SDS) or who seemed to develop pituitary dysfunction underwent provocative endocrine testing during a period of 3–36 months after SAH onset. The relationship between IGF-1 SDS and clinical factors of the patients such as severity of SAH, aneurysm location, and treatment modalities, were assessed. Six patients (10.2%) demonstrated their IGF-1 SDS less than −2. Multiple logistic regression analyses revealed that patients who underwent surgical clipping had a significantly lower IGF-1 SDS (<−1 SD) than patients who underwent endovascular embolization with an odds ratio of 5.83 ($p = 0.032$). Thirty-three patients took provocative tests and five (15.6%) patients were identified as having GHD. The mean IGF-1 SDS of these five GHD patients was 0.08 SD. The aneurysms in all GHD patients were located in internal carotid artery (ICA) or anterior cerebral artery (ACA). To the best of our knowledge, this is the first report describing the prevalence of GHD in Japanese patients after aSAH, and it was not as high as that of previous European studies. We recommend that screening pituitary dysfunction for aSAH survivors with their aneurysms located in ICA or ACA.

1. Introduction

hypothalamic–pituitary dysfunction has been reported in 37.5–55.5% of patients after aneurysmal subarachnoid hemorrhage (aSAH) [1–5]. This recently identified high prevalence has increased interest in the development of improved pituitary functional assessment in the management of aSAH survivors. As for the mechanism of pituitary dysfunction in patients after aSAH, the initial hemorrhage, increased intracranial pressure with brain edema, and surgical intervention can all potentially damage the hypothalamic–pituitary axis. Post-SAH symptoms such as general fatigue and depression are similar to symptoms of hypopituitarism, so neurosurgeons may not consider evaluating a patient's pituitary function if a patient has had a good neurological outcome after aSAH. A recent study revealed that even patients with good neurological outcomes have neuroendocrine dysfunction after aSAH [6]. Assessment of pituitary function in patients after aSAH and a method for identifying patients at particularly high risk of developing pituitary dysfunction are needed.

Previous studies have confirmed that GHD is the most common brain injury-induced pituitary dysfunction [7–9]. To monitor growth hormone (GH) disorders in adulthood, the insulin tolerance test (ITT) is used for the diagnosis of GHD; however, it is impracticable to perform an ITT on all aSAH survivors. Therefore, patients who develop GHD after aSAH may often go undiagnosed. Because there have been no reports about hypothalamic–pituitary dysfunction after aSAH in Japanese patients, the purpose of the present study was to evaluate pituitary function in Japanese aSAH survivors and to elucidate the implicative factors in pituitary dysfunction in patients after aSAH.

* Corresponding author. Tel.: +81 6 6210 8435; fax: +81 6 6210 8434.
E-mail addresses: neurosaitoh@mbk.nifty.com, saitoh@nsurg.med.osaka-u.ac.jp (Y. Saitoh).

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2. Materials and methods

All consecutive 237 patients with aSAH admitted to the Department of Neurosurgery, Osaka University Hospital (OUH, n = 117) or to the Department of Neurosurgery, Hanwa Memorial Hospital (HMH, n = 120) between April 2006 and January 2012 were enrolled in the study. SAH was diagnosed by CT scanning, and aneurysm location was identified by CT angiography or four-vessel angiography. In both hospitals, more than two neurosurgeons discussed the preferable treatment modality, surgical clipping or endovascular embolization. Treatment modality was selected according to the aneurysmal form, aneurysmal location, and presence or absence of a hematoma. All treatments and subsequent therapies were managed by experienced neurosurgeons. Both hospitals integrated a neurointerventional unit as part of comprehensive neurosurgical management.

Inclusion criteria of this study were as follows: patients with (1) a modified Rankin scale (mRS) score of $\leqslant$4 at 3 months after SAH onset, and (2) regular follow-up after hospital discharge. Patients who underwent treatment with drugs affecting hypothalamic–pituitary function and patients with epileptic seizures, pre-existing endocrine disorder, liver failure, or renal failure were excluded. After screening the medical records, 59 patients were considered eligible for the study based on the inclusion criteria.

The following variables were recorded in all patients: age; sex; aneurysm location; treatment modality (surgical clipping or endovascular embolization); clinical SAH severity on admission to the hospital using the World Federation of Neurosurgical Societies (WFNS) grading system [10], the Hunt and Kosnik (H&K) grading system [11], and radiological classification of bleeding seen on brain CT scan using the Fisher classification [12]; and body mass index (BMI) at evaluating time. SAH-related complications, such as vasospasm and hydrocephalus, were also noted.

2.1. Endocrine evaluation

2.1.1. Evaluation of basal pituitary hormones

We had set the time window of SAH of more than 3 months but less than 36 months before endocrine testing. Endocrine testing was performed in all 59 patients between 9:00 and 11:00 AM, including measurement of the following hormones: Growth hormone (GH) (reference range, 0.0–2.7 ng/mL), cortisol (reference range, 4.3–20.0 μg/L), adrenocorticotropic hormone (ACTH) (reference range, 0–60 pg/mL), free tyroxine (FT4) (reference range, 0.8–1.6 ng/dL), free triiodotyronine (FT3) (reference range, 2.0–3.4 pg/mL), thyroid stimulating hormone (TSH) (reference range, 0.40–3.80 μU/L), testosterone (reference range, 2.86–8.06 ng/mL) in men, estradiol (reference range, 10–366 pg/mL) in women, luteinizing hormone (LH) (reference range, 1.2–6.5 mIU/L), follicle stimulating hormone (FSH) (reference range, 2.0–13.0 mIU/L), prolactin (PRL) (reference range, 3.8–20.5 ng/mL), and IGF-1. Secondary adrenal insufficiency was defined as a morning plasma cortisol concentration of <3 μg/L [13]. Hypogonadism was defined as follows: in men, testosterone <3.5 ng/mL without elevated gonadotropins in the presence of normal PRL [14]; in premenopausal women, lack of menstrual bleeding since the onset of aSAH or low estradiol along with normal PRL; and in postmenopausal women, low serum LH and/or FSH for age [15]. Secondary hypothyroidism was diagnosed if FT4 was less than 0.8 ng/dL and TSH was not elevated. The diagnosis of hyperprolactinemia was based on PRL levels above 20.5 ng/mL in men and 33.0 ng/mL in women. GH insufficiency was suspected in patients with low IGF-1 SDS for the age. For IGF-1, age-dependent standard deviation scores (SDS) were evaluated according to age-dependent reference ranges, which were published recently [16].

2.1.2. Provocating endocrine test

To evaluate pituitary axis insufficiency, we performed provocating endocrine tests such as ITT, thyrotropin-releasing hormone (TRH) test, and luteinizing hormone releasing hormone (LHRH) test for patients who showed low IGF-1 SDS, with informed consent. The informed consent was obtained from each patient after a full explanation of all the provocating endocrine tests. During these provocating endocrine tests, blood samples were obtained from 9:00 to 11:00 AM to measure cortisol, FT4, FT3, TSH, LH, FSH, PRL, and GH every 30 min. According to the Guidelines for the Diagnosis and Treatment of adult GHD in Japan [17], severe GHD and mild GHD were defined by peak GH responses to insulin tolerance testing of $\leqslant$1.8 ng/mL and $\leqslant$3.0 ng/mL, respectively.

The Research Ethics Committee of Osaka University Hospital approved this study (approval number: 10120). Informed consent was obtained from all patients.

2.2. Statistical analysis

To investigate which factors influenced the patients' IGF-1, we divided patients with an IGF-1 SDS < −1 from the others, because IGF-1 less than zero was considered as GH disorder in the clinical situation, and the mean IGF-1 SDS of all the patients was 0.03. We determined which variables were independently associated with low IGF-1 SDS after aSAH using multivariate analyses. Correlation coefficients assessed the relationships between variables such as age ($\geqslant$60 or <60), sex, clinical severity of SAH (WFNS grade $\geqslant$3 or <3), existence of vasospasm, and treatment modality (endovascular embolization or surgical clipping) and their effects on IGF-1 SDS (IGF-1 SDS < −1 SD or other). Analyses were performed using multiple logistic regression. As for clinical SAH severity, we divided the patients into groups according to a WFNS grade of $\geqslant$3 or <3 because a grade of 3 is the dividing line between alert patients and those with disturbance of consciousness. In all comparisons, $p < 0.05$ was considered statistically significant. All analyses were performed with JMP statistical software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Evaluation of basal pituitary hormones

There were 19 men and 40 women (31 postmenopausal and 9 premenopausal). The mean age at the time of pituitary function testing was 58.0 ± 13.5 years (range, 25–81 years). The clinical characteristics of these 59 patients, such as age, sex, aneurysm location, treatment modality, clinical and radiological SAH severity, complications (vasospasm and hydrocephalus), and body mass index (BMI), are shown in Table 1. Six patients (10.2%) had an IGF-1 SDS less than −2 SDS. Three patients had hyperprolactinemia. No patients showed secondary hypothyroidism, hypogonadism, or secondary adrenal insufficiency. Data are presented as the mean value ± SD or as medians.

3.2. Provocating endocrine test

Thirty-three patients underwent the provocating endocrine test and five (15.1%) patients demonstrated GHD (severe GHD: 1, mild GHD: 4). There was no other hormonal deficiency detected by provocating test. All the GHD patients had their aneurysms located in ICA (n = 3) or ACA (n = 2). Patients with their aneurysms located in ACA underwent surgical clipping, two of the patients with their aneurysms in ICA underwent endovascular embolization, and another had both treatments because of a history of aSAH history twice. As for the mRS, three of the five GHD patients showed their