Retrospective review of previous minor leak before major subarachnoid hemorrhage diagnosed by MRI as a predictor of occurrence of symptomatic delayed cerebral ischemia

Shinri Oda, MD,¹ Masami Shimoda, MD,¹ Akihiro Hirayama, MD,¹ Masaaki Imai, MD,¹ Fuminari Komatsu, MD,¹ Hideaki Shigematsu, MD,¹ Jun Nishiyama, MD,¹ Kazuko Hotta, MD,¹ and Mitsunori Matsumae, MD²

¹Department of Neurosurgery, Tokai University Hachioji Hospital, Tokyo; and ²Department of Neurosurgery, Tokai University School of Medicine, Kanagawa, Japan

OBJECTIVE This study attempted to determine whether a previous minor leak correlated with the occurrence of symptomatic delayed cerebral ischemia (sDCI).

METHODS The authors retrospectively evaluated sDCI-related clinical features and findings from MRI, including T1-weighted imaging (T1WI)–FLAIR mismatch at the time of admission, in 151 patients admitted with subarachnoid hemorrhage (SAH) within 48 hours of ictus.

RESULTS The overall incidence of sDCI was 23% (35 of 151 patients). In all subjects, multivariate analysis revealed that World Federation of Neurosurgical Societies Grades II–V, age 70 years or older, presence of rebleeding after admission, a previous minor leak before the major SAH attack as diagnosed by T1WI–FLAIR mismatch, acute infarction on diffusion-weighted imaging, and CT SAH score were significantly associated with occurrence of sDCI. In patients with no previous minor leak before major SAH as diagnosed by T1WI–FLAIR mismatch, the incidence of sDCI was only 7% (7 of 97 patients).

CONCLUSIONS A previous minor leak before major SAH as diagnosed by T1WI–FLAIR mismatch represents an important sDCI-related factor. When the analysis was restricted to patients with true acute SAH without a previous minor leak diagnosed by T1WI–FLAIR mismatch, the incidence of sDCI was extremely low.

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KEY WORDS delayed cerebral ischemia; magnetic resonance imaging; minor leak; subarachnoid hemorrhage; vascular disorders

IN patients with aneurysmal subarachnoid hemorrhage (SAH), a preceding minor leak can only be suggested by the presence of a warning headache as disclosed by the patient, family, and/or caregivers during the admission interview. However, poor clinical condition and recall bias can cause inaccuracy. We developed a neuro-radiological method to diagnose previous minor leakage before major SAH based on findings from MRI at the time of admission. A previous minor leak before major SAH was determined by the presence of clearly detected bright hyperintense subarachnoid blood (BHSB) on T1-weighted imaging (T1WI) accompanied by SAH blood on FLAIR images distributed over a larger area than BHSB on T1WI (T1WI–FLAIR mismatch).¹⁶

The development of symptomatic delayed cerebral ischemia (sDCI) after aneurysmal SAH represents the most important complication after SAH and has a major impact on patient outcomes. Several predictors for the occurrence of sDCI have been reported, such as the amount of SAH clot,^{3,24} clearance of SAH clot,¹⁸ additional intracerebral hemorrhage (ICH),¹⁷ and intraventricular hemorrhage.^{4,11} However, the occurrence of sDCI cannot be reliably predicted for the individual patient. We therefore retrospectively reviewed patients with aneurysmal SAH who underwent treatment at our hospital to assess whether MRI findings at the time of admission suggest risk factors for the occurrence of sDCI. This study aimed to assess the association of a previous major leak before major SAH

ABBREVIATIONS BHSB = bright hyperintense subarachnoid blood; DWI = diffusion weighted imaging; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; sDCI = symptomatic delayed cerebral ischemia; T1WI = T1-weighted imaging; WFNS = World Federation of Neurosurgical Societies. **SUBMITTED** July 31, 2016. **ACCEPTED** October 13, 2016.

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attack as diagnosed by T1WI-FLAIR mismatch and the occurrence of sDCI, as when experimental SAH-induced vasospasm is induced with the use of a 2-hemorrhage model.¹⁴ We hypothesized that a previous minor leak has a predictive value for the occurrence of sDCI.

Methods

Patient Population

Subjects were selected from the 240 patients in the non-traumatic acute-phase aneurysmal SAH database at our hospital who had been treated between September 2002 and December 2015. Among these patients, we identified 151 patients who had undergone adequate MRI, including diffusion-weighted imaging (DWI), FLAIR imaging, T1WI, and CT on admission and were admitted within 48 hours of SAH onset. Clinical and imaging records were evaluated retrospectively. Study approval was obtained from the institutional review board for clinical research at our university.

Primary End Point

In principle, the primary end point was the occurrence of sDCI, which was defined as any new ischemic lesion on serial DWI studies or DWI studies obtained at the time of clinical deterioration. Similarly, when new infarction attributable to sDCI was not confirmed on DWI, we defined the apparent angiographic vasospasm at the time of clinical deterioration as sDCI.

Imaging Protocol

Patients with aneurysmal SAH routinely undergo serial MRI on admission, within 2–7 days after surgery, and before discharge. In addition, MRI was used for diagnosis of cerebral infarction due to sDCI at the time of clinical deterioration. At all time points, serial MRI included axial conventional T1WI, FLAIR, DWI, and MR angiography and was performed using a 1.5-T superconducting magnet (Signa EXCITE or HDX, GE Medical Systems) with a quadrature head coil. Pulse sequences were collected according to our previously reported parameters.¹⁶

All patients underwent 3D CT angiography to identify ruptured aneurysms and estimate early vasospasm of major vessels. MRI was performed only after obtaining informed consent from the patient and/or a relative. Initial MRI at the time of admission was performed before conventional angiographic, surgical, or endovascular procedures in all cases.

Surgical Procedure and Patient Management

Patients with SAH in the acute stage underwent craniotomy or intravascular surgery within 72 hours after SAH onset. With the exception of patients with Fisher Grade 1 or 2 SAH based on CT findings at the time of admission, indicating no or only a small hematoma, all patients underwent cisternal or lumbar drainage. All patients were administered fasudil hydrochloride intravenously for 7–21 days postoperatively as prophylaxis against sDCI. The 100 most recent patients also received oral cilostazol (200 mg/

day) for 7–21 days postoperatively. Hypervolemic therapy was administered according to previously reported protocols.²⁰

Definitions of Variables

All patients were graded on admission according to the World Federation of Neurosurgical Societies (WFNS) grading system.² SAH severity was classified using CT findings according to the Fisher grading system.³ SAH observed on CT was scored semiquantitatively according to the methods outlined previously⁸ as the sum of scores ranging from 0 to 3 for each of 10 cisterns: 0, no blood; 1, small amount of blood in SAH; 2, moderate amount of blood in SAH; and 3, SAH completely filled with blood. We added analysis of bilateral convex sulci, so a total of 12 cisterns were investigated (CT SAH score). These scores were totaled to create an SAH sum score ranging from 0 to 36.

Warning headache was defined as a sudden and unusually severe headache lasting at least 1 hour, followed by a symptom-free interval or marked improvement of symptoms before admission for major SAH. The presence of a warning headache was identified in thorough admission interviews of patients and their relatives or accompanying individuals.

Among patients with T1WI-detected clear BHSB on admission MRI, if the distribution of SAH on T1WI (T1WI BHSB component) almost entirely matched the distribution of SAH on FLAIR (FLAIR hyperintense component), the patient was diagnosed with subacute SAH that was not associated with rebleeding¹⁶ and was thus excluded from the study. In the remaining patients with T1WI-detected BHSB, the distribution of subarachnoid blood on FLAIR images over a larger area than the BHSB on T1WI (T1WI-FLAIR mismatch) was taken as an indication of new, acute SAH. T1WI-detected BHSB in these patients represents subacute SAH due to a previous minor leak.¹⁶ If FLAIR-detected SAH had no T1WI-detected BHSB on admission MRI, the SAH was considered acute.

On the admission MRI study, high-intensity lesions visible on DWI that showed low signal intensity in the lesion on apparent diffusion coefficient mapping were defined as DWI-detected early infarction at the time of SAH onset.¹⁹

Diagnosis of ICH was defined as a collection of blood more than 1 cm in diameter detected by CT. Rebleeding after admission was defined as a definite increase in the volume of blood visible on CT accompanied by sudden deterioration of the level of consciousness compared with baseline MRI or CT findings on admission.

In principle, sDCI was defined as clinical deterioration with new infarction detected by DWI (serial DWI or DWI at the time of deterioration). Even if a patient with clinical deterioration did not exhibit new cerebral infarction on DWI, we diagnosed sDCI when distinct angiographic vasospasm was evident on neuroradiological images. Clinical deterioration caused by sDCI was defined as a new neurological deterioration that included focal deficit, decline in level of consciousness, or either transient or permanent motor paresis. A decreased level of consciousness was defined as a ≥ 2 -point decrease in the Glasgow Coma Scale score within a 24-hour period.²³ For the detection of

FIG. 1. Flow diagram of patient selection. h = hours.

vasospasm, transcranial Doppler ultrasonography was not routinely performed. Instead, all patients who experienced clinical deterioration underwent 3D CT angiography or conventional digital subtraction angiography to determine the presence of vasospasm and rule out other causes of deterioration (e.g., hydrocephalus, rebleeding, cerebral edema, seizure, infection, or metabolic disturbance).^{22,23} Based on findings on immediate postoperative CT, serial MRI, or MRI at the time of clinical deterioration, infarction after SAH accompanied by sDCI was distinguished from lesions of primary brain damage that had occurred at the time of aneurysm rupture or surgery-related complications, such as contusion, local brain edema caused by retraction,¹⁰ or infarction due to occlusion of parent arteries or perforators after aneurysm clipping or coiling.

CT and MRI findings were interpreted by at least 2 senior stroke neurosurgeons (M.S. and S.O., with 33 and 28 years of experience, respectively). In the case of disagreement between raters, the diagnosis was determined by consensus decision.

Outcome was assessed at 3 months using the modified Rankin Scale (mRS).²¹ Patients were stratified into favorable outcome (mRS Scores 0–2) or unfavorable outcome (mRS Scores 3–6). Postoperative management was

conducted in accordance with previously reported protocols.^{19,20}

Statistical Analysis

Clinical factors potentially associated with occurrence of sDCI were analyzed using Fisher's exact test for categorical variables and an independent sample 2-tailed Student t-test for continuous variables (age, CT SAH score). All clinical factors with a significance level of $p < 0.05$ by univariate analysis were subjected to multivariate logistic regression analysis, with occurrence of sDCI as the dependent variable. Statistical analyses were performed using SPSS for Windows version 22.0 (IBM).

Results

Participants

Among the 240 patients treated between September 2002 and December 2015, we excluded 13 who received conservative therapy instead of surgery due to the absence of brainstem reflexes and 17 with SAH due to ruptured dissecting aneurysms (Fig. 1). The remaining 210 patients underwent acute-stage aneurysm surgery via craniotomy

TABLE 1. Clinical features and neurological status on admission

Variable	Total	Value*		p Value
		w/ sDCI	w/o sDCI	
No. of patients	151	35 (23)	116 (77)	
Warning sign				
Yes	15	2 (6)	13 (11)	0.523
No	62	4 (11)	58 (50)	<0.001
Unknown	74	29 (83)	45 (39)	<0.001
Age (yrs)				
Mean $\pm$ SD	61 $\pm$ 14	67 $\pm$ 13	60 $\pm$ 14	0.008
Range	21–89	42–86	21–89	
≥ 70 yrs	48	19 (54)	29 (25)	0.002
Female sex	106	28 (80)	78 (67)	0.206
Rebleeding after admission	32	15 (43)	17 (15)	0.001
WFNS grade on admission				
I	90	9 (26)	81 (70)	<0.001
II–V	61	26 (74)	35 (30)	<0.001
IV & V	32	15 (43)	17 (15)	0.001

* Values represent number (%) unless stated otherwise. Percentages in the "no. of patients" row are based on the total number of patients, and the remaining percentages in the "w/ sDCI" and "w/o sDCI" columns are based on the number of patients with and without sDCI, respectively.

or an interventional procedure within 72 hours of SAH onset. Among these 210 patients, we identified 151 patients admitted within 48 hours of SAH onset who underwent adequate MRI, including DWI, FLAIR, T1WI, and CT on admission. These 151 SAH patients showed stable vital signs, reflecting adequate respiration and circulation, and they underwent serial MRI and CT after admission.

Outcome Data

The overall incidence of sDCI was 23.2% (35 of 151 patients) (Table 1).

Main Results

Symptomatic DCI, Clinical Features, and Neurological Status

Table 1 summarizes the preoperative clinical features that differed significantly between patients with and without sDCI. The incidence of sDCI was significantly higher in elderly SAH patients (≥ 70 years old) and patients with disturbance of consciousness (WFNS Grade II–V) or rebleeding after admission.

The incidence of warning headache was low (10%) and was not associated with occurrence of sDCI. The incidence of sDCI was significantly lower among the 62 patients (41%) who reported no history of warning headache before admission. Among the 74 patients (49%) in whom the presence or absence of warning headache was unknown, the incidence of sDCI was significantly higher (Table 1).

Symptomatic DCI and Neuroradiological Features on Admission

Table 2 summarizes the neuroradiological features on admission that differed significantly between patients with and without sDCI. The incidence of sDCI was significantly

TABLE 2. CT and MRI features on admission

Variable	Total	Value		p Value
		w/ sDCI	w/o sDCI	
No. of patients	151	35 (23)	116 (77)	
CT findings				
Fisher Grade 3	107	33 (94)	74 (64)	<0.001
CT SAH score, mean $\pm$ SD	17 $\pm$ 10	26 $\pm$ 7	14 $\pm$ 10	<0.001
ICH	30	12 (34)	18 (16)	0.027
Intraventricular hemorrhage	78	29 (83)	49 (42)	<0.001
MRI findings				
Acute hydrocephalus	78	31 (89)	47 (41)	<0.001
T1WI-FLAIR mismatch	54	28 (80)	26 (22)	<0.001
Acute infarction on DWI	16	11 (34)	5 (4)	<0.001
Periventricular WML	37	17 (49)	20 (17)	0.001
Deep WML	62	21 (60)	41 (35)	0.011
Old infarction	24	11 (31)	23 (20)	0.006
DWI-detected SAH on basal cistern	99	33 (94)	66 (57)	<0.001
DWI-detected SAH on convexity	54	26 (74)	28 (24)	<0.001
DBS on FLAIR	50	26 (74)	28 (24)	<0.001
Aneurysm site				
Anterior communicating artery	48	15 (43)	33 (28)	
Anterior cerebral artery	8	1 (3)	7 (6)	
Internal carotid artery	50	10 (29)	40 (35)	
Middle cerebral artery	34	7 (20)	27 (23)	
Posterior circulation	11	1 (3)	10 (7)	0.458
Aneurysm size				
≥ 5 mm	86	19 (54)	67 (58)	0.846
≥ 10 mm	11	4 (11)	7 (6)	0.283

DBS = diffuse brain swelling; WML = white matter lesion.

Values represent number (%) unless stated otherwise. Percentages in the "no. of patients" row are based on the total number of patients, and the remaining percentages in the "w/ sDCI" and "w/o sDCI" columns are based on the number of patients with and without sDCI, respectively.

higher in patients with T1WI-FLAIR mismatch. Among 54 patients with T1WI-FLAIR mismatch, 24 were ≥ 70 years old. Among these elderly patients, 16 had sDCI.

Symptomatic DCI, Surgery, and Subsequent Events

Table 3 summarizes the surgery and subsequent events that were significantly different between patients with and without sDCI. In 2 sDCI patients without delayed angiographic vasospasm, new cerebral infarction was confirmed on serial DWI. In 2 additional sDCI patients, although new infarction attributable to sDCI was not confirmed on serial DWI or DWI at the time of neurological deterioration, apparent angiographic vasospasm was identified. Conversely, 10 patients displayed new asymptomatic infarction on serial DWI and were not classified as showing sDCI.

Among patients with chronic hydrocephalus and poor

TABLE 3. Drug administration, surgery, and subsequent events

Variable	Total	No. of Patients		p Value
		w/ sDCI	w/o sDCI	
No. of patients	151	35 (23)	116 (77)	
Aneurysm surgery				
Craniotomy	122	28 (80)	94 (81)	1.000
Coiling	29	7 (20)	22 (19)	
Administration of cilostazol	100	25 (71)	75 (65)	0.543
Delayed angiographic vasospasm	49	33 (94)	16 (14)	<0.001
New infarction on serial DWI	43	33 (94)	10 (9)	<0.001
Chronic hydrocephalus*	69	26 (74)	43 (37)	<0.001
mRS Score 3–6 at 3 mos	52	29 (83)	23 (20)	<0.001

Values represent number (%) unless stated otherwise. Percentages in the "no. of patients" row are based on the total number of patients, and the remaining percentages in the "w/ sDCI" and "w/o sDCI" columns are based on the number of patients with and without sDCI, respectively.

* The incidence of chronic hydrocephalus was calculated for surviving patients.

prognosis (mRS Scores 3–6), the incidence of sDCI was significantly higher.

Clinical Factors Predicting sDCI in Multivariate Analysis

In all subjects, multivariate stepwise logistic regression analysis revealed that WFNS Grades II–V, age ≥ 70 years, and presence of rebleeding after admission as preoperative clinical factors, and T1WI-FLAIR mismatch, acute infarction on DWI, and CT SAH score as neuroradiological findings on admission were significantly associated with the occurrence of sDCI (Table 4).

Incidence of sDCI in Patients With No Previous Minor Leak Before Major SAH

Overall, in 97 of the 151 patients admitted within 48 hours of SAH onset who underwent adequate neuroradiological imaging, T1WI-FLAIR mismatch was not observed. Among these patients, the incidence of sDCI was only 7% (7 of 97 patients).

Discussion

Key Results

Symptomatic DCI and Neuroradiological Diagnosis of a Minor Leak Prior to Major Attack

Disclosure of a previous minor leak during the admission interview is known to often be inaccurate, as eliciting complete information from a patient in poor clinical condition is difficult.⁹ Unsurprisingly then, in our study, occurrence of sDCI did not correlate with the disclosure of a previous minor leak before major SAH. In contrast, a neuroradiologically diagnosed minor leak prior to major SAH using T1WI-FLAIR mismatch correlated significantly with the occurrence of sDCI as determined by multivariate analysis.

One possible reason for the significant correlation between sDCI and a previous minor leak would be the time lag between the onset of a minor leak and presentation to a hospital. Strictly speaking, at the time of admission due to major SAH, SAH patients with a previous minor leak

TABLE 4. Results of multivariate logistic regression analysis for the presence of a symptomatic delayed cerebral ischemia

Variable	OR	95% CI	p Value
Preop clinical factors			
WFNS Grades II–V	4.898	1.992–12.046	0.001
Age ≥ 70 yrs	2.725	1.149–6.452	0.023
Rebleeding after admission	2.571	1.010–6.536	0.047
Associated neuroradiological findings on admission			
T1WI/FLAIR mismatch	41.667	9.524–200	<0.001
Acute infarction on DWI	9.259	1.876–45.455	0.006
CT SAH score	1.221	1.117–1.337	<0.001

diagnosed by T1WI-FLAIR mismatch corresponded to a clinical group in the subacute phase. As a matter of course, initiation of prophylaxis for sDCI such as administration of fasudil hydrochloride and/or cilostazol, as validated management strategies for maintaining systemic euvolemia, is delayed in these patients. Furthermore, a previous minor leak before a major SAH attack will mean that obstruction of the subarachnoid space by the presence of blood, fibrin, and fibrous arachnoid adhesions will interfere with clearance of the SAH clot. This decreased clearance of the SAH clot will in turn facilitate the occurrence of sDCI.¹⁸

Patients who experience a minor leak prior to major SAH are experiencing rebleeding at the time of the major SAH. Experimental models have shown that rebleeding increases the incidence of vasospasm,^{14,25} however, little information is available regarding the complications of rebleeding, including effects on the development of sDCI in humans. Lord et al. reported that rebleeding after SAH is not associated with changes in the incidence of sDCI,¹³ however, the definition of sDCI used by Lord et al. was the presence of either symptomatic vasospasm or infarction on CT attributable to vasospasm. This definition of sDCI seems prone to inaccuracy, because evaluation of infarction accompanied by sDCI is difficult in the presence of additional brain damage after rebleeding identified on CT. Diagnosis of clinical deterioration due to sDCI is likewise difficult in the presence of poor neurological condition due to rebleeding. For patients with rebleeding, we consider DWI as necessary for a suitably accurate diagnosis of cerebral infarction accompanied by sDCI. In the results from the present study, in addition to a significant correlation between the occurrence of sDCI and a minor leak prior to major SAH as diagnosed by T1WI-FLAIR mismatch, rebleeding after admission also correlated significantly with the occurrence of sDCI. Our previous report¹⁶ and several past investigations^{1,6} identified a previous minor leak as a risk factor for rebleeding after admission because a fragile aneurysm that ruptured at the time of the minor leak will be prone to rebleeding. As a matter of course, the volume of SAH clot is increased in patients who experience rebleeding. Moreover, rebleeding after admission and a minor leak prior to the major SAH reportedly correlate with the occurrence of ICH.^{6,15,16} Both the volume of SAH clot^{3,24} and additional ICH¹⁷ are predictors of sDCI that have been reported.

Other sDCI-Related Clinical Factors

The relationship of age to the occurrence of sDCI remains controversial, and no definitive conclusions have yet been reached.⁷ In our previous report, a minor leak according to T1WI-FLAIR mismatch was significantly correlated with elderly SAH patients on multivariate analysis.¹⁶ We speculate that symptoms due to a minor leak would be milder in elderly patients than in younger SAH patients, because an increase in intracranial pressure may not occur even after aneurysmal rupture due to the age-associated enlargement of the subarachnoid space. Therefore, elderly SAH patients presenting to the hospital at the time of the first attack due to a minor leak could be relatively few, and they may often be brought to the hospital only following major SAH.¹⁶ As a result, we considered that significant sDCI may be more frequent among the elderly.

Fisher Grade 3 SAH was significantly associated with sDCI on univariate analysis but not on multivariate analysis. The resolution of CT scanning has greatly improved since the first publication of the Fisher scale, and thus detection of subarachnoid clots has also dramatically improved, and differentiation between Grades 2 and 3 has thus become difficult. In addition, the amount of SAH as determined by Fisher grade is gradually losing significance as a predictive factor for sDCI. On the other hand, a more quantitative method for calculating SAH score correlated significantly with the occurrence of sDCI on multivariate analysis.

The concept of early brain injury, referring to the immediate cerebral damage that occurs within the first 72 hours after SAH, has recently been suggested.¹² Early brain injury is a multifactorial process characterized by primary insults and secondary ischemia. Primary insults involve factors such as the rapid increase in intracranial pressure, decreased global cerebral blood flow, disruption of the blood-brain barrier, brain swelling, and cerebral microcirculatory disturbance.⁵ In our study, WFNS Grade II–V and acute infarction on DWI¹⁹ also correlated significantly with the occurrence of sDCI. While these clinical factors are among the indicators of primary insults involved in early brain injury after SAH, clarification of their relevance requires further clinical studies.

Limitations

In this report, we could not prove whether a previous hemorrhage as apparent on MRI really represents a minor leak. We therefore should have used the term “preceding rupture” rather than “minor leak.”

We routinely performed CT immediately postoperatively and serial MRI at admission and within 2–7 days of surgery. However, completely distinguishing sDCI-associated infarction from infarction due to aneurysm repair is difficult because artifacts from clips or coils are present to some extent.

Because nimodipine has not been approved for use as a calcium-channel antagonist for the prevention of sDCI in Japan, we were unable to administer this drug. Therefore, our results may not apply to stroke centers where nimodipine is used.

This was a retrospective, single-center study; these findings therefore require prospective validation in dependent cohorts before valid application in clinical practice can be considered.

dent cohorts before valid application in clinical practice can be considered.

Conclusions

A previous minor leak before major SAH as diagnosed by T1WI-FLAIR mismatch is an important sDCI-related factor. The incidence of sDCI was extremely low in patients with true acute SAH without a previous minor leak diagnosed by T1WI-FLAIR mismatch. Past studies of sDCI may have included both patients with pure acute SAH without a previous minor leak and SAH patients with a previous minor leak before SAH major attack.

Given the retrospective nature of this study and the fact that all patients were from a single center, prospective validation of the present findings in dependent cohorts is required before the findings can be generalized to the general patient population.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Shimoda, Oda, Matsumae. Acquisition of data: all authors. Analysis and interpretation of data: Shimoda, Oda, Matsumae.

Correspondence

Masami Shimoda, Department of Neurosurgery, Tokai University Hachioji Hospital, 1838 Ishikawa-machi, Hachioji, Tokyo 192-0032, Japan. email: mashimoda-nsu@umin.ac.jp.