

Perioperative and Long-term Outcomes of Carotid Endarterectomy for Japanese Asymptomatic Cervical Carotid Artery Stenosis: A Single Institution Study

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Abstract

As the recently developed medical treatments for asymptomatic cervical carotid artery stenosis (ACCAS) have shown excellent stroke prevention, carotid endarterectomy (CEA) should be carried out for more selected patients and with lower complication rates and better long-term outcomes. We have performed CEA for Japanese ACCAS patients with a uniform surgical technique and strict perioperative management. In this study, we retrospectively investigated the perioperative complications and long-term outcomes of our CEA series. A total of 147 CEAs were carried out in 139 Japanese ACCAS patients. All patients were routinely checked for their cardiac function and high risk coronary lesions were preferentially treated before CEA. All CEAs were performed under general anesthesia using a shunt system. The postoperative cerebral blood flow was routinely measured under continued sedation to prevent postoperative hyperperfusion. The 30-day perioperative morbidity rate was 2.04%, including a perioperative stroke rate of 0.68%. There were no perioperative deaths. With regard to the long-term outcomes of the 134 followed-up patients, 9 patients were dead and 5 patients suffered from strokes, including 2 patients with ipsilateral hemispheric ischemia. The annual rates of death, all stroke and ipsilateral ischemic stroke were 1.15%, 0.64%, and 0.25%, respectively. These results showed that the perioperative morbidity and mortality rates of our CEAs were lower than those in the previous large trials. Furthermore, the long-term outcomes of this series were favorable to those reported in the latest medical treatment trials for ACCAS patients. CEA may be useful for preventing ischemic stroke in Japanese ACCAS patients.

Key words: asymptomatic cervical carotid artery stenosis, carotid endarterectomy, single institution study

Introduction

Asymptomatic cervical carotid artery stenosis (ACCAS) has been considered to be a risk factor for ipsilateral ischemic strokes. Since the Asymptomatic Carotid Atherosclerosis Study (ACAS) had reported the efficacy of carotid endarterectomy (CEA) for ACCAS patients, CEA has been positively performed for ACCAS patients with over 60% stenotic lesions.¹⁾ The results of the Medical Research Council Asymptomatic Carotid Surgery Trial (MRC-ACST) in 2004 also showed the benefits of CEA for ACCAS.²⁾ These results have indicated that CEA with less than 3% perioperative morbidity and mortality will halve the

five-year ipsilateral stroke risk in ACCAS patients with 60% or greater stenosis.^{1,2)}

On the other hand, the recently introduced antiplatelet agents and antihyperlipidemic drugs have been demonstrated to effectively prevent strokes by randomized controlled trials (RCTs) in ACCAS patients.^{3,4)} For example, Abbott showed that the annual ipsilateral stroke rate in ACCAS patients with medical treatments was equivalent to that of patients with CEA.⁵⁾ Consequently, CEA for ACCAS patients might be indicated for more selected lesions and requires a lower complication rate and better long-term outcomes.

In spite of the fact that there have been many studies of CEA for Caucasian ACCAS patients, only few reports have been published for Asian ACCAS

patients. We have performed CEA for Japanese ACCAS patients with routine use of shunt system and strict perioperative management. In this study, we retrospectively investigated the perioperative and long-term outcomes of our CEA series.

Methods

I. Patients and indications for surgery

A total of 452 CEAs were carried out in 427 patients with cervical carotid artery stenosis at the Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, from 1999 to 2011. All patients were Japanese. Of the 452 CEAs, 147 were carried out in 139 ACCAS patients. ACCAS was diagnosed by carotid ultrasonography and/or magnetic resonance angiography (MRA). The carotid stenosis rate was estimated at the maximum stenosis site using three-dimensional computed tomographic angiography (3D-CTA). Additionally, the location of the carotid bifurcation and the distal end of the stenotic lesion were also estimated on 3D-CTA by comparing them with the cervical vertebral body. The term "symptomatic" was defined as referring to a patient who had experienced previous transient ischemic attacks (TIAs) such as hemiparesis, aphasia, visual symptoms (including amaurosis fugax) and cerebral infarction at the ipsilateral carotid artery territory. Therefore, patients with a loss of consciousness, vertigo, and ischemic events in the contralateral carotid artery or in the vertebrobasilar territory were categorized as being "asymptomatic."

The indications for CEA at our institution was a carotid artery stenosis rate over 60% estimated by the European Carotid Surgery Trial (ECST) method⁶⁾ with a progressive stenotic lesion and/or vulnerable plaque. The vulnerable plaques in imaging studies were indicated by the following: ulcer formation, an irregular surface, hypoechoic in ultrasonography, or hyperintense in T₁-weighted magnetic resonance images (MRIs).^{7,8)}

In this study, we investigated strokes, cardiovascular events, death, and other complications in the perioperative period (within 30 days) and after a long-term follow-up (over 1 year). The activity of daily living (ADL) of each patient was also estimated by the modified Rankin Scale (mRS) score before surgery, at 30 days after surgery and after a longer follow-up period.

II. Preoperative management

Cardiologists and anesthesiologists routinely checked the patient's general condition, including their cardiac and pulmonary function. When high-risk coronary lesions were found in ACCAS patients, they

were preferentially treated before CEA. In patients with bilateral ACCAS, the initial treatment side was determined by the following criteria: the side with more severely stenotic lesions and/or a more severely reduced cerebral blood flow (CBF) as determined by the cold xenon computed tomography (CT) method. Antiplatelet therapy was maintained until surgery using a single agent, such as aspirin (100 mg daily).

III. Surgical procedures

General anesthesia with propofol and fentanyl was used in all the patients. After general heparinization (intravenous 3,000–5,000 IU administration keeping the activated coagulation time over 200 seconds) and carotid cross-clamping, an arteriotomy was made from the common carotid artery to the internal carotid artery to expose the whole atheromatous plaque. A T-shaped silicone shunt system was routinely used.^{9,10)} The stenotic lesion was removed by meticulous dissection of the atheromatous plaque from the involved carotid wall using a microscope. Then, the arteriotomy was closed from the distal to proximal sites by a running suture. During this procedure, argatroban was topically applied at the CEA site to prevent local mural thrombus formation.¹¹⁾ The time required to place a shunt system was less than 5 minutes and to close the arteriotomy was less than 15 minutes.

IV. Postoperative management

The postoperative CBF was routinely measured to detect hyperperfusion by the cold xenon CT method under continued sedation after CEA.¹²⁾ In this study, hyperperfusion was defined as > 150% for the ipsilateral middle cerebral artery (MCA) territory CBF in comparison to the contralateral MCA territory CBF.¹²⁾ When hyperperfusion was detected in patients, sedation with propofol and/or dexmedetomidine was continued to strictly control the blood pressure (systolic blood pressure ranging from 110 mmHg to 140 mmHg) until normoperfusion was obtained in the ipsilateral MCA territory. Within 3 days after CEA, medical treatment including antiplatelet agents was started in all the patients. The long-term outcomes were checked by the scheduled (6 months and 12 months after CEA and then annually, thereafter) carotid ultrasonographic and physical examinations.

V. Statistical analysis

The 5- and 10-year stroke-free rates and survival rates were estimated using the Kaplan-Meier method. All data were calculated using a commercially available software package (JMP® 11.0, SAS Institute Inc., Cary, North Carolina, USA).

Table 1 Summary of the clinical features of the 147 carotid endarterectomies in 139 patients with asymptomatic cervical carotid artery stenosis

Mean age, y (range)	69 (47–81)	
Male/female	122/17	
Preoperative risk factors	n = 139	%
Hypertension	112	82.3
Diabetes mellitus	54	37.4
Cardiovascular disease	71	51
Hyperlipidemia	82	59.1
Chronic kidney disease	30	21
Chronic obstructive pulmonary disease*	27	21.7
Imaging characteristics	No. (range)	%
Left/right	78/69	
Mean stenotic rate (ECST)	82.8 (60–95)	
Mean bifurcation level	Lower C3 (middle C5–upper C3)	
Mean plaque length (mm)	29.5 (15.0–60.0)	
Mean distal end of plaque	C2/3 (middle C4–middle C2)	
Vulnerable plaque	120	81.6
Contralateral carotid stenosis (> 50%)	29	19.7

*Forced expiratory volume in 1 sec < 70%. ECST: European Carotid Surgery Trial.

Results

I. Clinical features

During the 13-year period from 1999 to 2011, 147 CEAs were carried out in 139 Japanese ACCAS patients. Eight of the 139 patients had bilateral ACCAS. Their clinical features are summarized in Table 1. The mean age was 69 years old (range, 47–81). Hypertension was the most frequently observed risk factor (present in > 80% of cases) followed by hyperlipidemia and cardiovascular disease (> 50%). The mean stenosis rate was 82.8% ± 11.1% (range, 60–95%). The carotid bifurcation was located at the lower C3 (C: cervical vertebra) on average ranging from the middle C5 to the upper C3 (Fig. 1). The mean plaque length was 29.5 mm (range, 15–60 mm). The distal end of the plaque was located at a location ranging from the middle C4 to the upper C2 (between C2 and C3 on average). More than 80% of lesions showed vulnerable plaques, including irregular walls, ulcer formation, and/or intraplaque hemorrhage (Table 1). The mean preoperative mRS score of the 139 ACCAS patients was 0.82 (range, 0–2).

II. Perioperative and long-term outcomes

There was no mortality (0%), but there were three morbidities (2.04%; Table 2). The three postoperative complications were composed of one ipsilateral

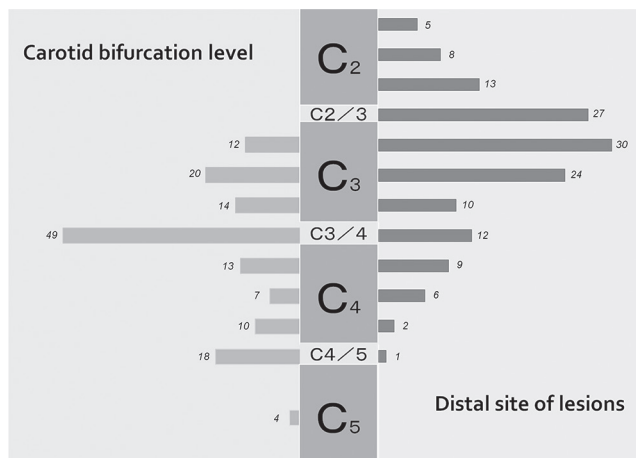


Fig. 1 Diagram showing the cervical vertebrae, the distribution of the carotid bifurcation levels, and the distal end of the plaque in surgical patients. The mean carotid bifurcation level is the lower border of C3, and the mean distal end of the stenotic lesion is the C2/C3 level. C: cervical vertebra.

infarction, one severe heart failure, and one cervical hematoma due to venous oozing blood. There was no hyperperfusion or myocardial infarction during the perioperative period. The mean mRS score at 30 days was 0.86 (range, 0–3). The causes of the reduced mRS score were only due to the surgical complications.

Among the 139 ACCAS patients who underwent CEA, 134 patients were followed-up for at least 12 months. All the followed-up patients received continuous antiplatelet agents, usually single agent aspirin 100 mg daily, for at least 1 year and medication therapy to control atherosclerotic risk factors. The follow-up period was 70.2 months on the average, ranging from 12 months to 168 months. The clinical outcomes during this period are summarized in Table 3. Nine (6.71%) patients died; four died of malignancies, two died of myocardial infarction, one died of renal failure, and the remaining two died due to unknown causes. Myocardial infarction was observed in a total of seven (5.22%) patients. Two (1.49%) patients presented with ipsilateral TIA and infarction. Another three (2.24%) patients showed strokes, including one contralateral infarction, one cerebellar infarction, and one intracerebral hemorrhage. The annual rates of ipsilateral ischemic stroke, all strokes, myocardial infarction, and death were 0.25%, 0.64%, 0.89%, and 1.15%, respectively. In our CEA cases for ACCAS, the 5- and 10-year stroke-free rates were estimated to be 96.4% and 89.6%, respectively,

and the 5- and 10-year survival rates were 94.6% and 87.9%, respectively (Fig. 2).

The mean mRS score at the latest follow-up was 1.56 (Table 4). The number of patients whose mRS scores were 0–2, 3–4, and 5–6 points were 110, 15, and 9, respectively. The causes of ADL worsening were seven malignancies, five cases with cardiovascular disease, three of renal failure, two strokes, two of dementia, two of diabetes mellitus-related disease, and two with undefined symptoms due to aging. Among these causes, the stroke-related symptoms were only four, and a total of 113 of the 117 monitored patients (96%) improved or maintained their neurological function at the latest follow-up (mean, 5.8 years).

During the follow-up period, seven sides of the 147 CEAs showed luminal restenosis from 60% to 95%, which was 73% on the average by ultrasonography. Fortunately, all restenotic lesions were asymptomatic and were treated by carotid artery stenting (CAS).

Table 2 Perioperative (30-days) morbidities and mortalities

	n = 147	%
Stroke	1	0.68
Myocardial infarction	0	0
Heart failure	1	0.68
Postoperative hyperperfusion	0	0
Cervical hematoma	1	0.68
Death	0	0
Total	3	2.04

Table 3 Clinical outcomes in long-term follow up (mean 70.2 months)

	n = 134	%	Estimated annual risk (%)
Ipsilateral infarction	2	1.49	0.25
All stroke	5	3.73	0.64
Ipsilateral TIA/infarction	2		
Contralateral infarction	1		
Cerebellar infarction	1		
Intracerebral hemorrhage	1		
Myocardial infarction	7	5.22	0.89
Death	9	6.71	1.15

TIA: transient ischemic attack.

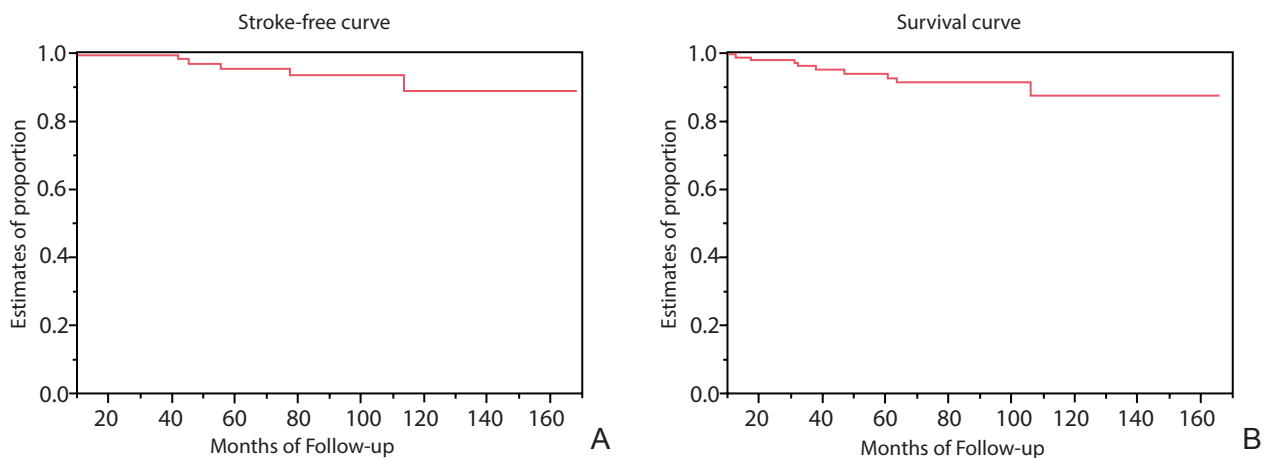


Fig. 2 The stroke-free (A) and survival curves (B) determined by Kaplan-Meier method. The 5- and 10-year stroke-free rates were 96.4% and 89.6%, respectively. The 5- and 10-year survival rates were 94.6% and 87.9%, respectively.

Discussion

In our series of 147 CEAs for ACCAS in 139 Japanese patients, there was no mortality and had a very low 2.04% morbidity rate. The results were favorable in comparison to the rates of the previous largest RCTs, such as the ACAS and MRC-ACST.^{1,2)}

Additionally, concerning the long-term outcomes, the annual rates of ipsilateral ischemic stroke, all strokes, and death were 0.25%, 0.64%, and 1.15%, respectively. These results also tended to be lower than those in the Second Manifestations of Arterial Disease (SMART) study, trying the best medical treatment for ACCAS patients.¹³⁾

In this series, we could successfully carry out CEA for the ACCAS patients, with a low incidence of perioperative strokes and death in comparison to the results of previous RCTs. For example, the risks of perioperative stroke and death in the ACAS,¹⁾ MRC-ACST²⁾ and our study were 2.3%, 2.8%, and 0.68%, respectively (Table 5). Our more favorable results were likely due to the following reasons: (1) The patients were routinely checked for their cardiac function by the specialists preoperatively. Previous reports have been shown that the risk of myocardial infarction in CEA for ACCAS patients is 0.6–1.4%.^{17,18)} Therefore, our patients with high risk coronary artery occlusive diseases were preferentially treated for their coronary diseases; (2) There were no adverse events related to postoperative hyperperfusion in this series. Generally, postoperative cerebral hyperperfusion syndrome after CEA occurs at the rate of 1–2%, and could lead to fatal events such as intracranial hemorrhage.^{12,19)} To prevent hyperperfusion and

hyperperfusion syndrome, we routinely measured the CBF immediately after CEA under continued sedation. Blood pressure was strictly controlled with continued sedation until normalization of the CBF;¹²⁾ and (3) We used a shunt system routinely to prevent ischemic stroke related to CBF reduction following carotid clamping. It could also account for low perioperative morbidity rate that CEA was performed by only a few expert operators (Y.O. & T.Y.). These were positive points associated with the fact that this was a single institution study.

Regarding the carotid stenotic lesions in Japanese patients, Toyota et al. previously revealed that the cervical carotid bifurcation level in the Japanese patients was higher than that in Hungarian patients based on carotid angiography.²⁰⁾ In the former patients, the cervical carotid bifurcation was located at the lower part of the third cervical vertebra (C3) and in the latter group at the middle part of the fourth cervical vertebra (C4). Additionally, in our patients, the distal end of the stenotic lesions was located between the second and the third cervical vertebra (C2–3). These data would indicate that the Japanese patients have more anatomical risk associated with CEA compared to Caucasian patients. Although CEA for these high position lesions was risky, we were able to successfully perform CEA by the following technique: (1) application of an omnidirectional retractor supporting ring to expose the cervical carotid artery,²¹⁾ (2) sufficient exposure of the hypoglossal nerve, (3) cutting the occipital artery if necessary, (4) routine use of a shunt system with a modified Sugita ring clip to facilitate holding the distal end of the shunt tube,¹⁰⁾ and (5) routine application of microscopy. These techniques made it possible to safely manage the high positional lesions extending to the second cervical vertebrae.⁹⁾

Table 4 Changes in 134 patient's modified Rankin Scale scores at 30 days postoperatively and at the latest follow-up

30-day		Latest follow-up examination				
mRS	n = 139			mRS	n = 134	
≤2	136	→	≤2	109	≤2	110
			3–4	14		
			5–6	8		
			unknown	5		
3–4	3	→	≤2	1	3–4	15
			3–4	1		
			5–6	1		
5–6	0				5–6	9
Mean	0.86			Mean	1.56	

mRS: modified Rankin Scale.

Table 5 A summary of a comparison of the perioperative stroke and death risk in previous studies. Some recently published series of CEAs for patients with ACCAS, especially from single institutions, demonstrated lower perioperative risk

Study	Stroke and death (%)
ACAS ¹⁾ (1995, US)	2.3
MRC-ACST ²⁾ (2004, UK)	2.8
Woo et al. ¹⁴⁾ (2010, US)	1.4
Scavee et al. ¹⁵⁾ (2001, Belgium) [†]	0.9
Ballotta et al. ¹⁶⁾ (2007, Italy) [†]	0
Our study (2014, Japan) [†]	0.68

[†]Study at a single institution.

Concerning the long-term outcomes of ACCAS patients, Abbott⁵⁾ analyzed 11 previous RCTs of ACCAS patients with medical treatment alone, and reported that the ipsilateral stroke rate had significantly decreased since the mid-1980s. And the best result among these RCTs was 0.83% of annual ischemic stroke rate in the SMART study,¹³⁾ which was lower than that of CEA in the ACAS trial.^{1,13)} According to studies for Japanese ACCAS patients treated with only medication, the Japan Carotid Atherosclerosis Study (JCAS)²²⁾ showed 2.7% of the 3-year ipsilateral stroke rate. Ogata et al.²³⁾ also reported 8.7% of the 5-year stroke rate in ACCAS patients treated medically. Since the benefit of CEA for ACCAS was not established, these studies did not recommend CEA to Japanese ACCAS patients. On the other hand, in our results, the annual rates of ipsilateral ischemic stroke and all strokes were 0.25% and 0.64%, respectively, that tended to be lower than previous studies. From our data, it would be suggested that complete CEA have a superior potential to reduce the long-term stroke risk in comparison to the best medical treatment.

CEA should be offered only to ACCAS patients who have a high risk of subsequent ischemic stroke. Our indication for CEA is a carotid artery stenosis rate over 60% with a progressive stenotic lesion and/or vulnerable plaque. It is because of the following reasons: the ACCAS patients with vulnerable plaques have been reported to have a much higher risk (hazard ratio 3.59–7.21) of ipsilateral ischemic events than those without vulnerable plaque, even when they have been treated with antiplatelet and lipid-lowering drugs.^{7,24,25)} In addition to the plaque pathology, progressive luminal narrowing is another important factor related to cerebral ischemic events.^{26,27)} Hirt showed significant relationships between the risk of ipsilateral ischemic events and the progression of luminal narrowing in ACCAS patients, and clarified that the annual progression of the carotid luminal narrowing by 10%, 20%, and 30% had the annual ipsilateral ischemic event rates of 6.3%, 18%, and 20%, respectively.²⁶⁾ Based on these reports, CEA would be more beneficial for the high risk ACCAS patients with vulnerable plaques or progressive stenosis.

Lately, CAS established a role of substitutional revascularization method for the patients with ACCAS. According to recent trials, outcomes of CAS were not inferior to those of CEA^{28,29)} just for ACCAS patients. There was a favorable trend for CAS in perioperative stroke, myocardial infarction, and death in patients with high surgical risk such as restenosis after CEA.²⁸⁾ On the other hand, CAS has disadvantages in the patients with severe arterial

tortuosity and/or calcified lesion in comparison to CEA. Additionally, CAS is risky in the patients with arterial dissection and vulnerable lesions, and has bradycardia and hypotension due to baroreflex at the carotid sinus.³⁰⁾ Therefore, CEA may be an indispensable treatment for ACCAS patients in the future. And a proper patient selection is required for CEA or CAS in the optimal treatment of ACCAS patients.

In our follow-up results, almost 90% of the patients were stroke-free and improved or maintained their ADL during the long periods. Even though CEA might have long-term benefits for preventing ischemic stroke, 10% of patients showed deterioration of their ADL during the long-term follow-up periods. The main causes responsible for this deterioration were not stroke, but other comorbidities such as malignancies, cardiovascular disease, or deterioration of their primary illness. The result indicates that general healthcare is therefore essential to maintain the long-term ADL after CEA for ACCAS patients.

Some limitations were present in this study. First of all, our study was retrospective single institution study, and data collection is performed by us. The statistical power of our findings might not be strong. Second, since we gave first priority to CEA, we did not have adequate data of the patients treated with best medical treatment or CAS. This presented difficulties in comparing CEA with other treatment modalities in our own cases.

For further issues, it is essential to define the stroke high-risk ACCAS patients who benefit from CEA. Asymptomatic Carotid Surgery Trial-2 (ACST-2)³¹⁾: an international randomized trial in Europe to prevent stroke for ACCAS is currently in progress. In Japan, Carotid Asymptomatic Stenosis Registry has been conducted from 2009, which is a prospective multicenter study to clarify long-term outcomes of CEA, CAS, and medical treatment only for ACCAS patients. It is hoped that current studies will provide the guidelines for treatment of patients with asymptomatic carotid artery stenosis.

Conclusion

In our CEA series with using a shunt system for Japanese ACCAS patients, the perioperative morbidity and mortality rates were low in comparison to those in previously reported RCT data. Preoperative routine cardiac check, strict blood pressure control to prevent hyperperfusion syndrome, and the safety procedure for high positional lesion were prerequisite for reducing perioperative comorbidities. The long-term ipsilateral ischemic stroke rate was favorable compared to that with medical treatment. Although the therapeutic

strategies for ACCAS are still controversial, this study suggests that CEA would be beneficial to prevent ischemic stroke in Japanese ACCAS patients with a high risk of future stroke. Further studies are required to establish the optimal indications for CEA in ACCAS patients.

Conflicts of Interest Disclosure

None of the authors have any conflicts of interest (COI) associated with this study. All authors who are members of The Japan Neurological Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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