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Original Article

Correlation between Higher Brain Dysfunction and Cerebral Blood Flow after Carotid Artery Stenting

Ryousuke Orimoto,[1] Eiichi Kobayashi,[2] Midori Abe,[3] Akihiko Adachi,[4] Yoichi Yoshida,[2] Tsubasa Okuyama,[5] and Yasuo Iwadate[2]

Objective: This study investigated the changes in higher brain function and cerebral blood flow (CBF) after carotid artery stenting (CAS), the relationship with CBF, and the impact of high intensities in diffusion-weighted imaging (DWI) after CAS.
Methods: We performed CAS between September 2017 and September 2019 in our department in 88 patients. Patients who did not undergo higher brain function tests according to our protocol or those who did not consent to participate in our study were excluded. This study targeted the 26 patients who were able to undergo the tests, including the Kana Pick-out Test (KPOT) II, three times: before, 1 week after, and 1–3 months after CAS. We investigated the chronological changes in higher brain function and their relationship with high intensity on DWI.
Results: The results of Symbol Digit Modalities Tests (SDMT) and KPOT I and II improved significantly. There was a significant correlation between the improvement of higher brain function and CBF in patients with stenosis exceeding 60%, a score of the Mini-Mental State Examination (MMSE) of 26 or less, and without other cause of higher brain dysfunction, including known dementia. High-intensity spots on DWI after CAS had no significant impact on higher brain function.
Conclusion: Higher brain function associated with attention and working memory improved significantly after CAS. There was a correlation between the improvement of higher brain function and CBF in patients with severe stenosis, mild cognitive impairment, and no known dementia. The prevention of subsequent ischemic attack and higher brain function should both be taken into account when performing CAS.

Keywords▶ higher brain function, carotid artery stenting, hemodynamics

Introduction

To prevent the onset of ischemic stroke, treatment for internal carotid artery stenosis is performed based on evidence from the North American Symptomatic Carotid Endarterectomy (NASCET), Asymptomatic Carotid Atherosclerosis Study (ACAS), and Stent and Angioplasty with Patients at High Risk for Endarterectomy (SAPPHIRE). On the other hand, in clinical practice, there are sometimes patients in whom higher brain dysfunction decreases after surgery. Changes in cerebral blood flow (CBF) after treatment may influence higher brain function. Several studies investigated this issue. However, neuropsychological tests differed among the studies and the results were not consistent. We examined the following points in patients in whom carotid artery stenting (CAS) was performed in our department: (1) changes in higher brain function after surgery on assessment using a testing battery established by combining conventional neuropsychological tests, (2) the relationship between changes in CBF and those in higher brain function based on single-photon emission computed tomography (SPECT) after CAS, and (3) the influence of a high-signal-intensity area on a diffusion-weighted imaging (DWI) after surgery on higher brain function.

[1]Kimitsu Central Hospital, Kisarazu, Chiba, Japan
[2]Department of Neurological Surgery, Chiba University Hospital, Chiba, Chiba, Japan
[3]Rehabilitation Medicine, Chiba University, Chiba, Chiba, Japan
[4]Department of Neurosurgery, Narita Red Cross Hospital, Narita, Chiba, Japan
[5]Department of Neurosurgery, Higashi Chiba Medical Center, Togane, Chiba, Japan

Received: June 25, 2020; Accepted: December 20, 2020
Corresponding author: Ryousuke Orimoto. Department of Neurosurgery, Kimitsu Central Hospital, 1010, Sakurai, Kisarazu, Chiba 292-8535, Japan.
Email: orimotoryousuke@gmail.com

Materials and Methods

In patients with carotid artery stenosis, the percent stenosis was measured using the NASCET method, and treatment was indicated for those with ≥50% symptomatic stenosis or ≥80% asymptomatic stenosis. Of 88 patients in whom CAS was performed in the Department of Neurosurgery, Chiba University Hospital between September 2017 and September 2019, the subjects were 26, excluding 3 in whom paralysis or aphasia made neuropsychological tests difficult, 3 who developed hyperperfusion syndrome, making neuropsychological test implementation in accordance with the protocol impossible, 1 in whom staged angioplasty was performed, violating the protocol, 4 from whom informed consent regarding participation in this study was not received (including withdrawal during this study), 43 for whom three sessions of neuropsychological testing were unable to be conducted due to difficulties in schedule adjustment, early discharge, referral to other hospitals, or moving, and 8 who were unable to complete the Kana Pick-out Test (KPOT) II (**Fig. 1**).

CAS was performed under sedation and local anesthesia. In general, double balloon protection was adopted for the prevention of embolism. An Optimo (Tokai Medical, Kasugai City, Aichi, Japan) or Flowgate 2 (Stryker, Kalamazoo, MI, USA) was inserted to the proximal side of the lesion, and a Guardwire (Medtronic, Minneapolis, MN, USA) was inserted to the distal side. Predilatation was conducted (omitted when a stent was able to be passed through the site of stenosis). After stent deployment at the site of stenosis, postdilatation was performed. Using an aspiration catheter, blood was aspirated until debris disappeared and protection was released. Intravascular ultrasonography (IVUS) was performed to confirm the presence of plaque protrusion. When plaque protrusion was observed, an additional stent was inserted if necessary. In all patients, CAS was successful and there were no neurological complications.

The higher brain function test was conducted before surgery, 1 week after CAS, and after 1–3 months (total: three times).

(1) *Higher brain function test*

A testing battery consisted of the Mini-Mental State Examination (MMSE), Raven's Coloured Progressive Matrices (RCPM), Symbol Digit Modalities Test (SDMT), Trail Making Test (TMT), and KPOT I and II, which were determined by consultation with speech therapists belonging to our hospital to comprehensively evaluate higher brain function.

The MMSE consists of 11 question items: orientation, memory, calculating ability, linguistic competence, and graphical ability. It is conducted as a screening test for cognitive function.[1] The RCPM consists of 36 issues (12 × 3). Each subject must find the regularity of diagrams presented and select an appropriate diagram that applies to a blank column. The number of correct answers and time required are evaluated. This test is carried out to investigate cognitive function and non-language-mediated visual space cognition.[2] In the SDMT method, figures 1–9 are assigned to 9 diagrams, and each subject must apply figures corresponding to randomly arranged diagrams. The total number of questions is 110 and a larger number of responses is required in 90 seconds. The achievement rate is calculated by dividing the number of correct answers by the total number of questions. The distributivity of attention is evaluated.[3] In the TMT Part A method, figures of 1–25 randomly described on a piece of paper must be connected with lines in order. In the TMT Part B method, figures of 1–13 and hiragana letters of "a" to "shi" are randomly described, and each subject must alternately connect figures with hiragana letters (1 → "a" → 2 → "i"). The time until accomplishment is assessed. Continuous attention, visual exploration, visual motor cooperativeness, and working memory are evaluated.[4] In the KPOT I method, five letters: "a," "i," "u," "e," and "o," must be picked up from randomly arranged hiragana letters in 2 minutes. The number of works, number of correct answers, and picking errors (missing/mis-picking) are evaluated. In the KPOT II method, the above five letters must be picked up in 2 minutes while reading a story written in hiragana letters. In addition to the above items, each subject is asked about the content of the story after completion to evaluate expression. Attention, working memory, and concurrent processing are assessed.[5]

For statistical analysis, we used Excel Statcel4 add-in software (Microsoft) (OMS Publishing Inc., Tokyo, Japan). A p value of 0.05 was regarded as significant. The raw score was evaluated on MMSE, the total score on RCPM, the achievement rate on SDMT, and the time required on TMTs Part A and B. On KPOTs I and II, the correct answer rate was calculated by dividing the number of correct answers by the number of works.

To compare the results of respective tests before surgery, 1 week after surgery, and after 1–3 months, the Quade test was conducted as a paired multi-group difference test. When there was a significant difference, the Wilcoxon signed-rank test was performed between two points: before surgery vs. 1 week after surgery, 1 week after surgery vs. 1–3 months after surgery, and before surgery vs. 1–3 months after surgery.

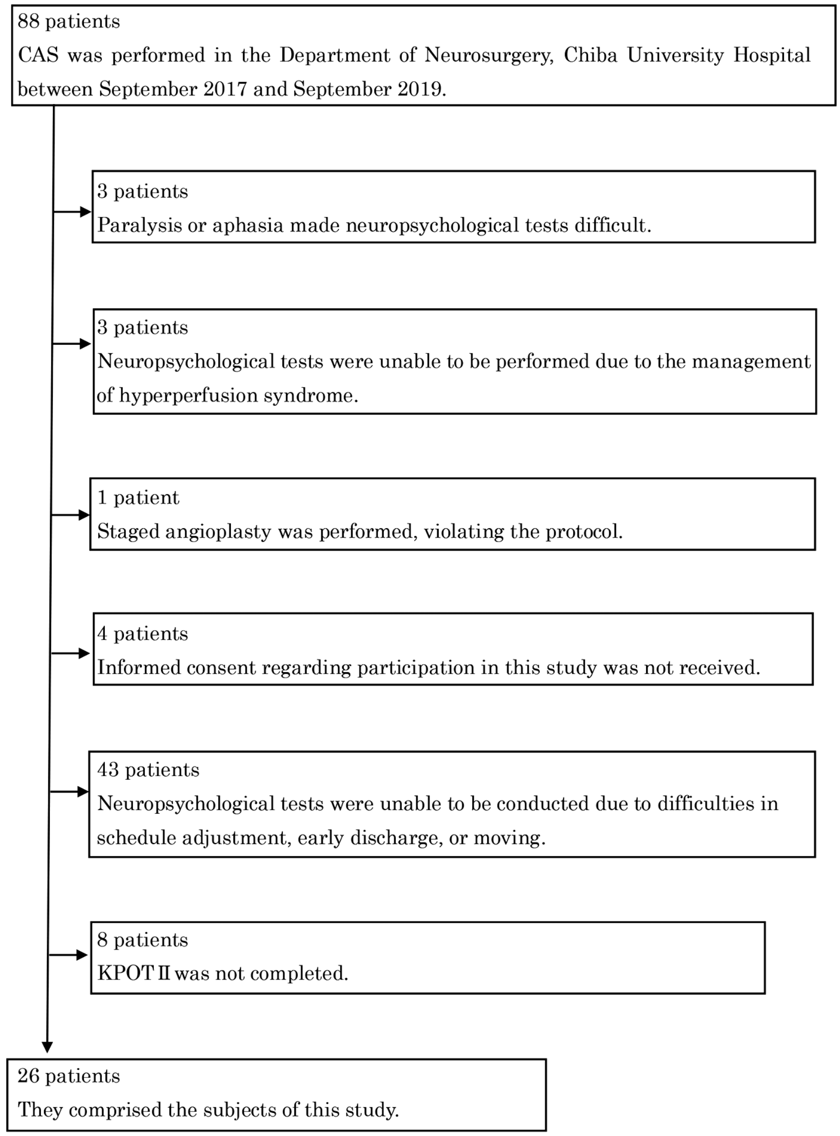

Fig. 1 Patients in whom CAS was performed in the Department of Neurosurgery, Chiba University Hospital between September 2017 and September 2019 are summarized in this tree diagram. CAS: carotid artery stenting

(2) *Changes in CBF and higher brain function*

CBF testing was performed using the ^{123}I-IMP-graph plotting method. In the absence of acetazolamide loading, 111 MBq of ^{123}I-IMP was intravenously administered before measurement. When performing acetazolamide loading, 1 g of acetazolamide was intravenously injected 15 minutes later, and the same dose of ^{123}I-IMP was administered after 10 minutes, followed by measurement. Information was collected over 2 seconds per frame for 2 minutes. The matrix size was 128 × 128. Before CAS, acetazolamide loading was conducted and images were prepared using the IMP-RAMDA method, in which the IMP-graph plotting method was combined with the serial distribution estimation method.[6] Loading-free CBF testing was conducted the day after CAS.

The ipsilateral cerebral hemisphere/cerebellar blood flow ratio was calculated. After calculating the pre-/post-treatment (1–3 months) correct answer rate ratio on KPOT II, the correlation with CBF was examined. We investigated 13 patients with <60% stenosis of the internal carotid artery (NASCET method) and an MMSE score of ≥27, excluding those with dementia.

(3) *Appearance of positive findings on DWI and higher brain function*

DWI-magnetic resonance imaging (MRI) was performed using a Signa EXCITED HD × 1.5T (GE Healthcare

Table 1 Serial changes in the results of neuropsychological tests after CAS

Examination	Before surgery	1 week after surgery	1–3 months after surgery	P (Quade)	P (Wilcoxon)		
					Before surgery and 1 week after surgery	1 week after surgery and 1–3 months after surgery	Before surgery and 1–3 months after surgery
MMSE	27 (25-29)	29 (26-29)	28 (25-30)	0.17	–	–	–
RCPM	28 (25-30)	28 (25-29)	28 (26-30)	0.47	–	–	–
SDMT	29 (26-31)	28 (26-34)	32 (25-35)	0.008*	0.09	0.25	0.009*
TMT-A	53 (46-74)	55 (41-79)	52 (37-72)	0.20	–	–	–
TMT-B	152 (110-215)	129 (115-202)	128 (96-163)	0.13	–	–	–
KPOT I	0.73 (0.64-0.85)	0.86 (0.75-0.91)	0.88 (0.73-0.89)	0.0004*	0.0008*	0.18	0.006*
KPOT II	0.64 (0.58-0.76)	0.67 (0.54-0.77)	0.77 (0.63-0.88)	0.006*	0.66	0.007*	0.001*

The results of each neuropsychological test before surgery, 1 week after surgery, and after 1–3 months are expressed as the median and interquartile range. *P value <0.05. P (Quade): P value (Quade test). P (Wilcoxon): P value (Wilcoxon signed-rank sum test). CAS: carotid artery stenting; KPOT: Kana Pick-out Test; MMSE: Mini-Mental State Examination; RCPM: Raven's colored progressive matrices test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test

Japan), Discovery MR750 3.0T (GE Healthcare Japan), Intera-Achieva 1.5T (Philips Electronics Japan), or Ingenia 3.0T (Philips Electronics Japan). For DWI, the echo-planar method was used, establishing the b value as 1000 s/mm^2.

The subjects were divided into two groups: a group in which a high-signal-intensity area was detected on DWI after surgery (DWI-positive group) and a group in which there was no high-signal-intensity area (DWI-negative group), and were analyzed. In each group, the Quade test was performed to compare the KPOT II results before surgery, 1 week after surgery, and after 1–3 months. When there was a significant difference, the Wilcoxon signed-rank test was performed between two points: before surgery vs. 1 week after surgery, 1 week after surgery vs. 1–3 months after surgery, and before surgery vs. 1–3 months after surgery.

The rate of change was calculated by dividing the KPOT II results 1–3 months after surgery by those before surgery. A previous study involving young healthy adults reported that the rates of change in the correct answer rate on KPOT II were ±3.8% in persons aged 20–29 years and approximately ±9.9% in those aged 30–39 years.[7)] In this study, slight changes were also evaluated as being within the permissible range; patients with a ± ≤5% change between the values before surgery and 1–3 months after surgery were regarded as exhibiting no change, those with a smaller rate of change as exhibiting a decrease, and those with a larger rate of change as exhibiting an increase. The rate of change in CBF on SPECT was evaluated regarding ±5% as a reference.

Results

The subjects of this study consisted of 16 with symptomatic lesions and 10 with asymptomatic lesions. The mean age was 73.6 ± 7.9 years. There were 24 males and 2 females.

(1) *Higher brain function test*

The results of each neuropsychological test are shown in **Table 1**. On the Quade test, there were significant differences in the results of SDMT, KPOT I, and KPOT II (SDMT: 29 vs. 28 vs. 32, respectively, P = 0.008, KPOT I: 0.73 vs. 0.86 vs. 0.88, respectively, P = 0.0004, and KPOT II: 0.64 vs. 0.67 vs. 0.77, respectively, P = 0.006). To investigate two points between which there were significant differences on the three neuropsychological tests, the Wilcoxon signed-rank test was conducted. On SDMT, there was a significant improvement between two points: before surgery and 1–3 months after surgery (29.10 vs. 32.25, respectively, P = 0.009). On KPOT I, there were significant improvements between two points: before surgery

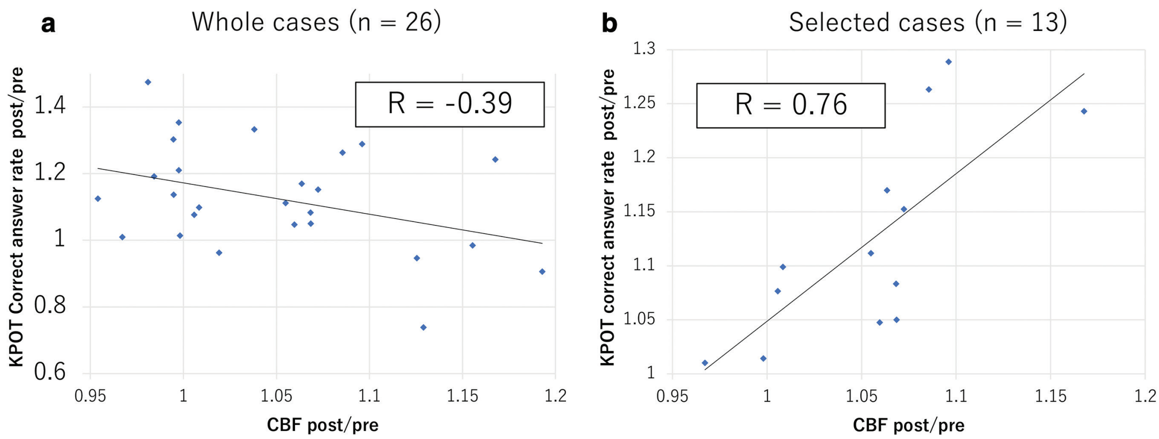

Fig. 2 Relationship between changes in CBF after CAS and those in the correct answer rate on KPOT II. As the transverse axis, the ipsilateral cerebral hemisphere/cerebellar blood flow ratio before surgery was plotted. As the longitudinal axis, the pre-/post-treatment correct answer ratio on KPOT II was plotted. Left: whole case (2a). Right: selected cases (2b). CAS: carotid artery stenting; CBF: cerebral blood flow; KPOT II: Kana Pick-out Test II

and 1 week after surgery, and between before surgery and 1–3 months after surgery (0.73 vs. 0.86, respectively, P = 0.0008, 0.73 vs. 0.88, respectively, P = 0.006). On KPOT II, there were significant improvements between two points: 1 week after surgery and 1–3 months after surgery, and between before surgery and 1–3 months after surgery (0.67 vs. 0.77, respectively, P = 0.007, 0.64 vs. 0.77, respectively, P = 0.001).

(2) *Changes in CBF and higher brain function* (**Fig. 2**)
The relationship between changes in CBF after CAS and those in the results of KPOT II in the 26 patients is shown in **Table 2**. In the 26 patients (**Fig. 2a**), there was no correlation between the two parameters (correlation coefficient: –0.39). When the above 13 patients were excluded (**Fig. 2b**), there was a positive correlation (correlation coefficient: 0.76, coefficient of determination: 0.58).

(3) *Appearance of positive findings on DWI and higher brain function*
Of the 26 patients, a high-signal-intensity area was detected on DWI after surgery in 16 (DWI-positive group), with a mean age of 71.1 ± 7.7 years. It was not detected in nine (DWI-negative group), with a mean age of 77.4 ± 7.1 years. In one, MRI was impossible after pacemaker insertion. In the DWI-positive group, there was no new neurological finding, such as paralysis or aphasia, after surgery, and lesions were asymptomatic in all patients.

The changes in the results of KPOT II in the DWI-positive and DWI-negative groups are shown in **Table 3**.

In the DWI-positive group, the Quade test was conducted among three points: before surgery, 1 week after surgery, and 1–3 months after surgery. There were significant differences (0.67 vs. 0.76 vs. 0.80, respectively, P = 0.002). In addition, the Wilcoxon signed-rank test was performed between two points. There were significant improvements in the correct answer rate between two points: 1 week after surgery and 1–3 months after surgery, and between before surgery and 1–3 months after surgery (0.76 vs. 0.80, respectively, P = 0.03, 0.67 vs. 0.80, respectively, P = 0.006). However, in 1 (6.25%) of the 16 patients, there was a reduction in the correct answer rate after CAS. In the DWI-negative group, the Quade test was also conducted. There were no significant differences among the three points (P = 0.32). However, there was an improvement or no change in the correct answer rate in individual patients; there was no reduction in any patient.

Discussion

Regarding higher brain function after CAS, there were significant improvements on SDMT, KPOT I, and KPOT II. On the three tests, there were improvements between two points: before surgery and 1–3 months after surgery. On KPOT I, early improvement was also noted. These tests consist of examination items for evaluating attention. However, improvement in the uni-processing power, such as the KPOT I items, is achieved relatively early, whereas a specific time may be required until improvements in items requiring the distributivity of attention or concurrent processing capacity, such as the SDMT and KPOT II items, are achieved. Patients with internal carotid artery stenosis often have mild higher brain dysfunction, which does not affect daily living.[8] To detect mild higher brain dysfunction and evaluate its changes, weakly loaded screening tests are not appropriate. On SDMT, KPOT II, and TMT Part B,

Table 2 Changes in CBF after CAS and those in the correct answer rate on KPOT II

Case	Percent stenosis (%)	CBF				Correct answer rate on KPOT II			
		Before surgery	After surgery	After/before surgery	Change	Before surgery	After surgery	After/before surgery	Change
1	60	0.85	0.86	1.01	→	0.65	0.71	1.10	↑
2	79	0.78	0.90	1.16	↑	0.81	0.80	0.98	→
3	68	0.91	0.99	1.09	↑	0.75	0.95	1.26	↑
4	68	0.97	1.03	1.06	↑	0.77	0.90	1.17	↑
5	73	0.97	1.01	1.04	→	0.60	0.80	1.33	↑
6	70	1.13	1.11	0.98	→	0.62	0.91	1.47	↑
7	74	0.88	0.89	1.02	→	0.57	0.55	0.96	→
8	75	0.85	0.84	0.99	→	0.63	0.72	1.14	↑
9	51	0.98	0.98	1.00	→	0.64	0.87	1.35	↑
10	63	0.91	0.89	0.98	→	0.47	0.56	1.19	↑
11	73	0.87	0.93	1.07	↑	0.76	0.80	1.05	→
12	84	0.89	0.94	1.05	→	0.71	0.79	1.11	↑
13	85	0.81	0.86	1.06	↑	0.75	0.79	1.05	→
14	84	0.96	0.97	1.01	→	0.59	0.63	1.08	↑
15	61	0.85	0.91	1.07	↑	0.64	0.73	1.15	↑
16	67	0.99	0.98	0.99	→	0.68	0.89	1.30	↑
17	56	0.83	0.93	1.13	↑	0.85	0.63	0.74	↓
18	90	0.67	0.80	1.19	↑	0.48	0.43	0.91	↓
19	87	1.10	1.10	1.00	→	0.73	0.74	1.01	→
20	62	0.93	1.08	1.17	↑	0.72	0.89	1.24	↑
21	72	0.97	0.94	0.97	→	0.90	0.91	1.01	→
22	80	0.99	1.09	1.10	↑	0.52	0.67	1.29	↑
23	63	1.00	1.07	1.07	↑	0.57	0.62	1.08	↑
24	55	0.83	0.83	1.00	→	0.79	0.96	1.21	↑
25	71	0.80	0.90	1.13	↑	0.96	0.91	0.95	→
26	59	1.09	1.04	0.95	→	0.62	0.69	1.13	↑

Changes in cerebral blood flow after CAS and those in the correct answer rate on KPOT II are expressed as follows, regarding ±5% as no change: increase: ↑, no change: →, and decrease: ↓. CAS: carotid artery stenting; CBF: cerebral blood flow; KPOT: Kana Pick-out Test

memory retention and processing are conducted in parallel, activating working memory; the level of loading is slightly strong. Working memory is defined as a system to temporarily retain information required for complex cognitive tasks, such as language understanding, learning, and reasoning, and operations.[9] In particular, it is associated with the frontal/parietal lobe cortex.[10] Working-memory-activating tests facilitate the detection of relatively mild higher brain dysfunction and may be useful for evaluating higher brain function before and after treatment for carotid artery stenosis. A previous study involving relatively young subjects (70.9 ± 7.5 years) with asymptomatic carotid artery stenosis reported that TMT Part B significantly improved higher brain function.[11] However, especially in elderly persons, there are many dropout cases; this test was not appropriate for assessment in this study. MMSE is useful as a screening test for dementia, but its sensitivity is low in evaluating mild higher brain dysfunction.[12–14] It was not appropriate for testing in this study. TMT Part A is also useful for evaluating attention, but the level of loading is weak for subjects; in this study, it may have been impossible to detect changes in higher brain function.

One reason why the results of higher brain function testing after revascularization differed among previous studies was the timing of follow-up.[15] However, the results may

Table 3 Changes in the correct answer rate on KPOT II in the DWI-positive and DWI-negative groups

	Cases	Median correct answer rate (interquartile range)			P (Quade)	P (Wilcoxon)		
		Before surgery	1 week after surgery	1–3 months after surgery		Before surgery and 1 week after surgery	1 week after surgery and 1–3 months after surgery	Before surgery and 1–3 months after surgery
DWI-positive	16	0.67 (0.60–0.76)	0.76 (0.66–0.78)	0.80 (0.66–0.90)	0.002*	0.10	0.03*	0.006*
DWI-negative	9	0.64 (0.58–0.72)	0.62 (0.51–0.69)	0.75 (0.72–0.80)	0.320	–	–	–

To compare changes in the correct answer rate on KPOT II among 3 points, the Quade test was conducted. When there was a significant difference, the Wilcoxon signed-rank test was performed between two points. *P value <0.05. P (Quade): P value (Quade test). P (Wilcoxon): P value (Wilcoxon signed-rank sum test). DWI: diffusion-weighted image; KPOT II: Kana Pick-out Test

depend on the timing of evaluating subtle changes in higher brain function.

Four patients (Cases 9, 17, 24, and 26) had <60% stenosis according to the NASCET method, and it was not considered to cause a reduction in CBF. In the case of symptomatic internal carotid artery stenosis, CAS is sometimes performed to treat moderate stenosis, which does not influence CBF. However, postoperative improvement in higher brain function may not be achieved in patients without a reduction in CBF before surgery. Ching et al. compared the results of treatment among three groups: a group in which CAS was not successful despite a reduction in CBF, a group in which CAS was successful, with a reduction in CBF, and a group in which CAS was successful, with no reduction in CBF. They reported that improvement in higher brain function was achieved only in the second group.[16] Similarly, the preoperative MMSE score was ≥27 in eight patients (Cases 2, 6–8, 10, 11, 16, and 25), and higher brain hypofunction was absent or markedly mild on other tests. In Case 18, other tests suggested dementia, suggesting no improvement in higher brain function even if improvement in CBF was achieved. In patients without higher brain hypofunction before surgery, there may be no further improvement in higher brain function after CAS. When dementia-related brain hypofunction is present, differing from higher brain hypofunction related to a reduction in CBF, there may be no change in higher brain function after CAS. Thus, we examined changes in CBF on SPECT and the correct answer rate on KPOT II, excluding patients who were preoperatively considered to have no improvement in higher brain function. There was a correlation between the two parameters. Briefly, when there is a reduction in CBF related to marked stenosis of the internal carotid artery in the absence of higher brain dysfunction related to other etiologies, the relief of stenosis may increase CBF, improving cerebral metabolism and higher brain function.

Several studies reported that higher brain dysfunction persisted for a long period or permanently when microembolism developed.[17–21] However, Rafat et al. found no association between the appearance of a high-signal-intensity area on DWI after surgery and higher brain hypofunction.[22] In this study, the KPOT II results significantly improved even in the DWI-positive group. However, deterioration was noted in one patient in this group, suggesting that the appearance of predominant-side cerebral infarction is involved in higher brain hypofunction. In the DWI-negative group, there was no deterioration in any patient. According to several studies, the incidence of microembolism during

CAS is 20–40%.[23,24] We cannot exclude the possibility that it plays a role in postoperative higher brain hypofunction; intraoperative embolism prevention is important. However, the appearance of many micro high-signal-intensity areas on DWI may not affect higher brain function.

In the DWI-negative group, there were no significant differences in higher brain function among three points: before surgery, 1 week after surgery, and 1–3 months after surgery. However, in this group, many patients in whom an improvement in higher brain function may not be achieved, such as those without higher brain dysfunction and those with dementia, were included; type II errors may have been mixed.

As the limitations of this study, the possibility that repeated neuropsychological tests may lead to learning effects was indicated. Concerning KPOT, learning effects are not marked when the frontal lobe function is reduced. In particular, a specific period was established between the 2nd and 3rd higher brain function tests to exclude learning effects, but the subjects of this study included patients in whom learning effects cannot be ignored. In 4 (Cases 6, 8, 10, and 16) of the 26 patients presented in **Table 2**, marked improvements in the KPOT II results were achieved, although there were no changes in CBF after CAS. In the four patients, higher brain hypofunction was absent before surgery; learning effects may have been exhibited. As another limitation in this study, patients with symptomatic stenosis, those with asymptomatic stenosis, and those with bilateral stenosis were included in each group. More marked differences related to changes in higher brain function among these subgroups may be detected by conducting a multicenter cooperative study with a unified protocol.

Conclusion

After CAS, higher brain function, especially attention and working memory, improved in comparison with that before CAS. Regarding the association with CBF on SPECT, there was a correlation between improvement in CBF and that in higher brain function in patients with ≥60% stenosis in accordance with the NASCET method and a preoperative MMSE score of ≤26 (mild hypofunction) in the absence of dementia. Most high-signal-intensity areas on DWI after surgery were microlesions and there was no relationship with higher brain function.

Disclosure Statement

The authors declare no conflicts of interest.

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