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Postoperative Changes in Cerebral Metabolites Associated with Cognitive Improvement and Impairment after Carotid Endarterectomy: A 3T Proton MR Spectroscopy Study

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ABSTRACT

BACKGROUND AND PURPOSE: Cognitive function can improve or decline after carotid endarterectomy. Proton MR spectroscopy can be used evaluate cerebral metabolites, such as *N*-acetylaspartate, choline, and creatine, in vivo. The purpose of the present study was to determine whether postoperative changes in cerebral metabolites measured by using 3T proton MR spectroscopy were associated with changes in cognitive function after CEA.

MATERIALS AND METHODS: In 100 patients undergoing CEA for ipsilateral cervical internal carotid artery stenosis (≥70%), brain proton MR spectroscopy was performed before and after surgery. NAA/Cr and Cho/Cr ratios were measured in regions of interest placed in the centrum semiovale of both cerebral hemispheres. Neuropsychological testing was also performed preoperatively and 1 month postoperatively. Multivariate statistical analysis of factors related to postoperatively changed cognition was performed, and odds ratios with 95% confidence intervals were calculated.

RESULTS: On the basis of the neuropsychological assessments, 10 (10%), 80 (80%), and 10 (10%) patients were defined as having postoperatively improved, unchanged, and impaired cognition, respectively. A positive and high ΔNAA/Cr ratio (postoperative value–preoperative value) in the cerebral hemisphere ipsilateral to the operative site was significantly associated with postoperatively improved cognition (95% CI, 13.3–21.3; $P = .0016$). Negative and high absolute values of the ΔNAA/Cr ratio (95% CI, 0.018–0.101; $P = .0039$) and ΔCho/Cr ratio (95% CI, 0.042–0.135; $P = .0046$) in the ipsilateral cerebral hemisphere were significantly associated with postoperatively impaired cognition.

CONCLUSIONS: Postoperative changes in cerebral metabolites measured by using proton MR spectroscopy were associated with changes in cognitive function after CEA.

ABBREVIATIONS: CEA = carotid endarterectomy; CI = confidence interval; Rey test = Rey-Osterreith Complex Figure Test; WAIS-R = Wechsler Adult Intelligence Scale Revised

Carotid endarterectomy can reduce the risk of stroke in appropriately selected patients.[1,2] While CEA may also improve cognitive function,[3,4] cognitive impairment occurs in 10%–30% of patients following CEA.[5-8] A recent study reported that 11% of patients undergoing CEA experienced improvement in cognitive function after surgery, while another 11% experienced a decline in cognitive function after surgery.[9] Cerebral metabolism may also change along with these postoperative changes in cognitive function, but the relationship between these 2 factors remains unclear.

Proton MR spectroscopy enables noninvasive chemical analysis in vivo, because the proton is the most sensitive stable nucleus for MR spectroscopy and nearly all metabolites contain protons.[10] Proton MR spectroscopy can also measure relative changes in metabolites, including *N*-acetylaspartate, choline-containing compounds, and total creatine.[11] Investigators have suggested that the level of NAA in the brain is an index of neuronal viability[12] and that the level of choline in the brain is associated with membrane synthesis or degeneration in neural tissues.[13] On the basis of these hypotheses, proton MR spectroscopy has been applied for the study of various pathologic conditions of the cen-

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tral nervous system.[11,12,14-22] Several studies have also investigated relative changes in NAA and/or choline following CEA by using proton MR spectroscopy.[23-26] However, the clinical significance of such postoperative changes remains unknown.

Correlations between MR spectroscopic measures and neuropsychological function have been reported in patients with Alzheimer disease, mild cognitive impairment, idiopathic normal pressure hydrocephalus, and cerebral infarction.[14,17-22] Thus, the purpose of the present prospective study was to determine whether a postoperative increase or decrease in cerebral metabolites measured by using proton MR spectroscopy was associated with improvement or impairment in cognitive function after CEA.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria of Patients

We prospectively selected patients scheduled to undergo CEA and satisfying the following inclusion criteria: 75 years of age or younger; having ipsilateral cervical internal carotid artery stenosis (≥70%) on angiography with MR imaging, CT, or arterial catheterization according to the method of the North American Symptomatic Carotid Endarterectomy Trial[1]; having preoperative useful residual function (modified Rankin Scale, 0 or 1); the presence of episodes of ipsilateral carotid territory ischemic symptoms that had occurred between 2 weeks and 6 months before presentation to our department (defined as symptomatic carotid stenosis) or the absence of episodes of ipsilateral carotid territory ischemic symptoms or the presence of episodes of ipsilateral carotid territory ischemic symptoms that had occurred >6 months before presentation to our department (defined as asymptomatic carotid stenosis)[2]; having no infarction in the cerebral cortical area perfused by ≥1 branch of the middle cerebral artery confirmed by MR imaging, including T2-weighted and fluid-attenuated inversion recovery sequences, that was performed 2 weeks before surgery; and obtaining written informed consent. Patients who satisfied the following criteria after surgery were excluded from the present study: new neurologic deficits lasting for 2 weeks after surgery; and additional ischemic lesions on MR imaging, including T2-weighted and FLAIR sequences, performed 2 weeks after surgery compared with preoperative MR imaging. A 1.5T whole-body imaging system (Signa MR/i; GE Healthcare, Milwaukee, Wisconsin) was used for evaluation of ischemic lesions before and after surgery.

All study protocols were reviewed and approved by the local institutional ethics committee.

MR Spectroscopy

A 3T scanner (Signa Excite HD; GE Healthcare) with a "birdcage" quadrature head coil was used for this study. First, all subjects underwent axial T2-weighted imaging. In the T2-weighted images for each subject, 1 section through the upper gray matter above the centrum semiovale was selected, and a single-voxel region of interest was manually and symmetrically placed in the bilateral cerebral hemispheres so that the proportion of the cortical gray matter and CSF occupying the region of interest was as high and as low as possible, respectively (Fig 1). Voxel size was $17 \times 50 \times 15$ mm^3. Next, acquisition of proton MR spectroscopy

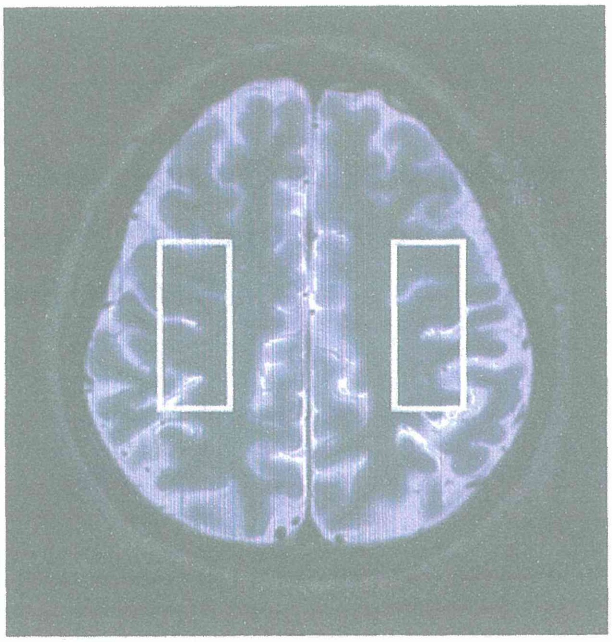

FIG 1. Regions of interest placed on 1 section through the upper gray matter above the centrum semiovale in an axial T2-weighted MR image to obtain MR spectroscopy.

was performed by using point-resolved spectroscopy with the following parameters: TR, 2000 ms; TE, 144 ms; data size, 4 K points; spectral width, 5000 Hz; 96 acquisitions (3.9 minutes). An area under each peak of 3 main metabolites was automatically obtained on the MR imaging console: choline-containing compounds at 3.2 ppm, total creatine at 3.0 ppm, and NAA at 2.0 ppm. Area ratios for NAA and Cho peaks were expressed as the relative ratio to Cr in each spectrum.

Patients underwent MR spectroscopy within 7 days before surgery and between 2 and 4 weeks after surgery. On each occasion, care was taken to place the region of interest in the same position on the T2-weighted image. NAA/Cr and Cho/Cr ratios in each cerebral hemisphere were calculated before and after surgery, and the difference between these 2 values (postoperative values minus preoperative values) was calculated and defined as ΔNAA/Cr and ΔCho/Cr ratios, respectively.

Neuropsychological Evaluation

For each patient, a battery of neuropsychological tests was administered, consisting of the Japanese translation of the Wechsler Adult Intelligence Scale Revised,[27] the Japanese translation of the Wechsler Memory Scale,[28] and the Rey test.[29] WAIS-R generates a verbal and performance intelligence quotient. The Rey test evaluates copy and recall of a complex figure. Thus, 5 scores (WAIS-R verbal IQ, WAIS-R performance IQ, Wechsler Memory Scale, Rey copy, and Rey recall) were used to evaluate cognitive function.

The neuropsychological tests were performed within 7 days before surgery and were repeated 1 month after surgery. All examinations were administered by a trained neuropsychologist who was blinded to the patient clinical information.

Postoperative cognition was categorized as improved, unchanged, or impaired for each patient on the basis of the definition described previously.[9] Briefly, 40 healthy volunteers served as controls and underwent the same neuropsychological tests on 2 separate occasions (intertest interval, 1–2 months).[9] Differences in each neuropsychological test score between the 2 tests (the second test score–the first test score) were calculated. For the neuropsychological test scores of patients undergoing CEA, a significant increment was defined as a postoperative test score greater than the preoperative score plus the value of the mean minus 2SDs of the difference between the 2 test scores in the controls; a significant decrement was defined as a postoperative test score less than the preoperative score minus the absolute value of the mean: 2SDs of the difference between the 2 test scores in the controls. A patient was defined as having postoperative cognitive improvement or impairment when there was a significant increment or decrement in ≥1 postoperative neuropsychological score, respectively; a patient was defined as having an unchanged cognition after surgery when there was no significant increment or decrement in any postoperative neuropsychological scores.[9]

Intraoperative Management

All patients underwent surgery under general anesthesia. An intraluminal shunt during ICA clamping was not used in any of the patients. The mean duration of ICA clamping was 37 minutes (range, 26–49 minutes).

Statistical Analysis

Data are expressed as the mean ± SD. Changes between the pre- and postoperative NAA/Cr or Cho/Cr ratio were evaluated by using the Wilcoxon signed rank test. Differences in the change of each neuropsychological test score among the controls and patients were evaluated by using the Mann-Whitney *U* test. Differences or incidences of each baseline characteristic among the 3 groups (patients with postoperatively improved, unchanged, or impaired cognition) were evaluated by using the χ^2 test followed by the Bonferroni inequality correction or the Scheffe F test. A multivariate statistical analysis of factors related to postoperatively improved or impaired cognition relative to postoperatively unchanged cognition was also performed by using a logistic regression model with odds ratios with 95% CIs calculated. Variables with $P < .2$ in the univariate analyses were selected for analysis in the final model. For all statistical analyses, significance was set at the $P < .05$ level. The only exception was the χ^2 test followed by the Bonferroni inequality correction, in which differences were deemed statistically significance if $P < .05/3 = 0.0167$.

RESULTS

During 36 months, 136 patients underwent CEA. Of these, 104 patients preoperatively satisfied the inclusion criteria. However, 2 patients experienced new major neurologic deficits that lasted 2 weeks after surgery; another 2 patients developed additional asymptomatic ischemic lesions on MR imaging, including T2-weighted and FLAIR sequences performed 1 month after surgery, compared with preoperative MR imaging. These 4 patients did not undergo MR spectroscopy and neuropsychological testing after surgery and were excluded. Thus, the remaining 100 patients were analyzed in the present study. None of these patients experienced further ischemic symptoms between initial evaluation and surgical intervention.

Table 1: NAA/Cr and Cho/Cr ratios before and after surgery[a]

	Before Surgery	After Surgery	P Value
NAA/Cr ratio			
Ipsilateral hemisphere	1.654 ± 0.195	1.660 ± 0.228	.2819
Contralateral hemisphere	1.720 ± 0.177	1.718 ± 0.190	.9694
Cho/Cr ratio			
Ipsilateral hemisphere	0.895 ± 0.109	0.888 ± 0.104	.3132
Contralateral hemisphere	0.868 ± 0.093	0.867 ± 0.095	.8760

[a] Values are expressed as means.

The mean age of the 100 patients (89 men, 11 women) studied was 68 ± 6 years (range, 52–75 years). Concomitant disease states and symptoms were recorded, including 88 patients with hypertension, 37 patients with diabetes mellitus, and 53 patients with dyslipidemia. Sixty-four patients had ipsilateral symptomatic ICA stenosis, and the remaining 36 patients had asymptomatic ICA stenosis. Preoperative MR imaging demonstrated infarction in the hemisphere ipsilateral to the ICA stenosis in 54 patients and no infarction in 46 patients. The overall average degree of ICA stenosis was 87.3 ± 8.8% with a range of 70%–99% according to the method of the North American Symptomatic Carotid Endarterectomy Trial.[1] The contralateral ICA was occluded in 6 patients, and 8 additional patients had 60%–99% stenosis.

The mean ± SD of NAA/Cr and Cho/Cr ratios in each cerebral hemisphere before and after CEA among 100 patients is summarized in Table 1. When we analyzed them as a group, none of these values differed between measurements before and after surgery.

Figure 2 shows the distribution of ΔNAA/Cr and ΔCho/Cr ratios in each patient in each cerebral hemisphere. The ΔNAA/Cr ratio ranged from −0.370 to 0.402 or from −0.190 to 0.303 in the cerebral hemisphere ipsilateral or contralateral to the operative site, respectively. The ΔCho/Cr ratio ranged from −0.170 to 0.204 or from −0.130 to 0.140 in the cerebral hemisphere ipsilateral or contralateral to the operative site, respectively.

On the basis of the neuropsychological assessments performed before and after surgery, 10 (10%), 80 (80%), and 10 (10%) patients were regarded as having postoperatively improved, unchanged, and impaired cognition, respectively. Table 2 shows differences in each neuropsychological test score between the 2 tests (the second test score–the first test score) in controls and patients. While none of these discrepancies differed between the controls and all patients or between controls and patients without a postoperative change in cognition, all the differences were higher in patients with postoperatively improved cognition and lower in those with postoperatively impaired cognition compared with the controls.

Table 3 shows the univariate analysis of patient characteristics among the 3 groups. The ΔNAA/Cr and ΔCho/Cr ratios in the cerebral hemisphere ipsilateral to the operative site statistically differentiated patients with postoperatively improved, unchanged, and impaired cognition. Specifically, ΔNAA/Cr and ΔCho/Cr ratios were higher in patients with postoperatively improved cognition and lower in those with postoperatively impaired cognition compared with patients without a postoperative change in cognition (Fig 2*A*). In addition, the ΔNAA/Cr ratio in the contralateral cerebral hemisphere was higher in patients with postoperatively improved cognition than in those with postoper-

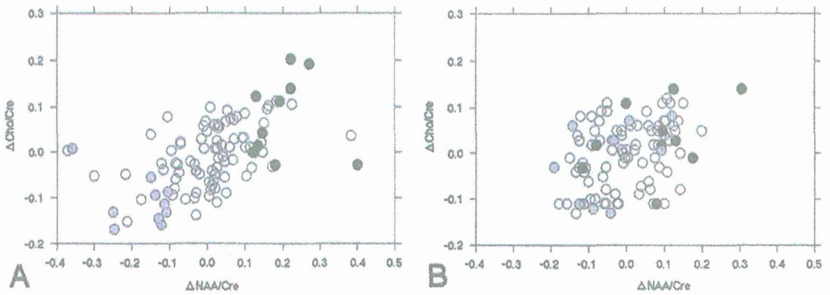

FIG 2. Distribution of ΔNAA/Cr and ΔCho/Cr ratios in each patient in the cerebral hemisphere ipsilateral (*A*) or contralateral (*B*) to the operative site. Closed, open, and half-tone circles indicate patients with postoperatively improved, unchanged, and impaired cognition, respectively.

atively unchanged or impaired cognition (Fig 2*B*). Other variables did not differ when comparing patients with postoperatively improved, unchanged, or impaired cognition. After we eliminated closely related variables in the univariate analyses, the following confounders ($P < .2$) were adopted in the logistic regression model for the multivariate analysis: age; ΔNAA/Cr ratio in each cerebral hemisphere; ΔCho/Cr ratio in the ipsilateral cerebral hemisphere for postoperatively improved cognition relative to postoperatively unchanged cognition; and ΔNAA/Cr and ΔCho/Cr ratios in the ipsilateral cerebral hemisphere for postoperatively impaired cognition relative to postoperatively unchanged cognition. Subsequent multivariate analysis revealed that positive and high ΔNAA/Cr ratios in the ipsilateral cerebral hemisphere significantly correlated with postoperatively improved cognition (95% CI, 13.3–21.3; $P = .0016$) and that negative and high absolute values of the ΔNAA/Cr ratio (95% CI, 0.018–0.101; $P = .0039$) and the ΔCho/Cr ratio (95% CI, 0.042–0.135; $P = .0046$) in the ipsilateral cerebral hemisphere significantly correlated with postoperatively impaired cognition.

Figures 3 and 4 show proton MR spectra in each patient with postoperative improvement or impairment in cognitive function, respectively.

DISCUSSION

The present study demonstrated that postoperative changes in cerebral metabolites measured by using proton MR spectroscopy were associated with changes in cognitive function following CEA.

Several studies have investigated changes in NAA/Cr and/or Cho/Cr ratios following CEA by using proton MR spectroscopy. While most of these studies reported increases in these values after CEA,[23-26] the remainder found no changes.[30] The variation in results between these studies may be from differences in methodologic factors, including the number of patients, types of patient, types of MR scanners, and the timing of postoperative assessment. In particular, previous studies have been performed by using devices operating at 1.5T and included a relatively smaller sample size (≤20 subjects).[23-26,30] The main advantages of proton MR spectroscopy at 3T over that at 1.5T include a higher signal-to-noise ratio, higher spatial and temporal resolutions, and better spectral resolution.[11] These advantages allow acquisitions of higher quality and result in a higher sensitivity for the detection of nervous system metabolites.[11] In the present study using a 3T imager and a large sample size, NAA/Cr and Cho/Cr ratios did not differ between measurements before and after CEA when they were analyzed as a group. Thus, NAA/Cr and Cho/Cr ratios usually do not change after CEA.

While numerous studies investigated changes in cognitive functioning following CEA by using neuropsychological testing,[3-8] there were no clear guidelines for determining significant improvement or impairment in cognition. This is because such changes may, in part, reflect the "practice effect" (an improvement in scores when patients are repeatedly tested).[3,7] In contrast, physicians or patients' families or both often report subjective postoperative improvement or impairment in cognition for patients undergoing CEA.[9] A recent study demonstrated that the optimal cutoff point of the degree of postoperative increase or decrease in neuropsychological test scores, such as the WAIS-R verbal IQ, WAIS-R performance IQ, Wechsler Memory Scale, Rey copy, and Rey recall, in detecting subjective improvement or impairment in cognition after surgery is identical to the mean + 2SDs or the mean − 2SDs, respectively, of the control value obtained from healthy subjects.[9] Furthermore, of patients with a postoperative increase in test scores more than the upper cutoff point or of those with a postoperative decrease in test scores less than the lower cutoff point in ≥1 neuropsychological test, 90% of patients in each group exhibited subjectively improved or impaired cognition, respectively, after surgery.[9] All patients with postoperative increases or decreases in test scores between the upper and lower cutoff points in all neuropsychological tests exhibited subjectively unchanged cognition after surgery.[9] Thus, in the present study, we determined significant postoperative improvement and impairment in cognition for each patient by using the same definition. As a result, 10% of patients who underwent CEA were defined as having postoperative improvement in cognition, and another 10% of patients who underwent CEA were defined as having postoperative impairment in cognition. These incidences were consistent with those from previous studies.[9]

The present study demonstrated that a postoperative increase and decrease in NAA/Cr ratios in the cerebral hemisphere ipsilateral to operative site were significantly associated with postoperative improvement and impairment in cognition, respectively. NAA is an amino acid found almost exclusively in neuronal cells, and the level of NAA in the brain may be an index of neuronal viability.[12] The NAA/Cr ratio also correlates with cerebral oxygen metabolism of the gray matter in patients with steno-occlusive carotid artery disease.[16] In addition, a decrease in the NAA/Cr ratio is associated with a decrease in cognitive function in elderly populations,[18,21] patients with cerebral infarction,[17,22] and those with Alzheimer disease.[20] Thus, the present data suggested that neuronal damage caused by CEA results in postoperative cognitive impairment. In contrast, in patients with idiopathic normal pressure hydrocephalus, a significant increase in the NAA/Cr ra-

Table 2: Differences in each neuropsychological test score between the 2 tests (the second test score–the first test score) in controls and patients[a]

Test	Controls[9] ($n = 40$)	All Patients ($n = 100$)	Subgroup: A) Improved Cognition ($n = 10$)	Subgroup: B) Unchanged Cognition ($n = 80$)	Subgroup: C) Impaired Cognition ($n = 10$)	*P* Value: Controls vs All Patients	*P* Value: Controls vs A	*P* Value: Controls vs B	*P* Value: Controls vs C
WAIS-R verbal IQ	3.4 ± 4.5	4.0 ± 6.2	11.4 ± 4.6	4.3 ± 5.1	−5.1 ± 4.0	.2377	<.0001	0.1117	<.0001
WAIS-R performance IQ	4.9 ± 5.0	4.7 ± 7.0	11.9 ± 4.3	5.2 ± 5.7	−6.7 ± 5.1	.5791	.0001	0.3582	<.0001
WMS	4.7 ± 6.1	3.7 ± 7.2	11.9 ± 4.8	4.3 ± 5.1	−9.4 ± 7.7	.4560	.0002	0.2678	<.0001
Rey copy	0.4 ± 1.1	0.8 ± 1.8	4.1 ± 1.4	0.7 ± 1.2	−1.9 ± 1.7	.0599	<.0001	0.0845	<.0001
Rey recall	2.9 ± 3.5	2.6 ± 4.3	7.5 ± 3.3	2.7 ± 3.6	−3.6 ± 2.8	.9796	.0007	0.7578	<.0001

Note:—WMS indicates Wechsler Memory Scale.

[a] Values are expressed as means.

Table 3: Comparison of characteristics among patients with postoperatively improved, unchanged, or impaired cognition

	Group: A) Improved Cognition ($n = 10$)	Group: B) Unchanged Cognition ($n = 80$)	Group: C) Impaired Cognition ($n = 10$)	*P* Value: A vs B	*P* Value: B vs C	*P* Value: C vs A
Age (yr) (mean)	64.9 ± 3.5	68.9 ± 6.2	67.9 ± 6.0	.1378	.8751	.5357
Male sex	90% (9/10)	89% (71/80)	90% (9/10)	>.9999	>.9999	>.9999
Hypertension	100% (10/10)	88% (70/80)	80% (8/10)	.5946	.6175	.4737
Diabetes mellitus	50% (5/10)	36% (29/80)	30% (3/10)	.4942	>.9999	.6499
Dyslipidemia	70% (7/10)	51% (41/80)	50% (5/10)	.3268	>.9999	.6499
Symptomatic lesion	60% (6/10)	63% (50/80)	80% (8/10)	>.9999	.4908	.6285
Infarction on preoperative MRI	40% (4/10)	55% (44/80)	60% (6/10)	.5053	>.9999	.6563
Degree of ICA stenosis (%) (mean)	88.0 ± 10.6	87.7 ± 8.2	83.0 ± 10.3	.9942	.2739	.4348
Bilateral lesions	20% (2/10)	13% (10/80)	20% (2/10)	.6175	.6175	>.9999
Duration of ICA clamping (min) (mean)	37.0 ± 5.0	37.2 ± 5.8	36.9 ± 6.2	.9940	.9870	.9992
ΔNAA/Cr ratio in ipsilateral hemisphere (mean)	0.201 ± 0.085	0.011 ± 0.112	−0.171 ± 0.085	<.0001	<.0001	<.0001
ΔNAA/Cr ratio in contralateral hemisphere (mean)	0.081 ± 0.122	−0.001 ± 0.092	−0.044 ± 0.098	.0428	.4108	.0169
ΔCho/Cr ratio in ipsilateral hemisphere (mean)	0.077 ± 0.088	−0.005 ± 0.063	−0.108 ± 0.053	.0013	<.0001	<.0001
ΔCho/Cr ratio in contralateral hemisphere (mean)	0.036 ± 0.079	−0.003 ± 0.070	−0.011 ± 0.082	.2786	.9430	.3465

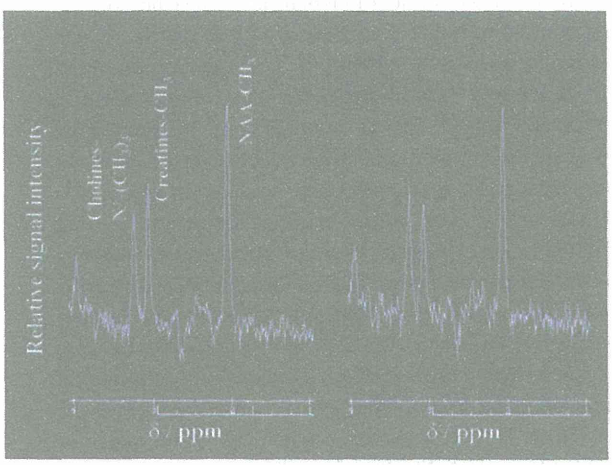

FIG 3. Proton MR spectra obtained by using point-resolved spectroscopy in the region of interest in the cerebral hemisphere ipsilateral to the operative site in a 62-year-old man with improved cognition after endarterectomy for symptomatic right internal carotid artery stenosis. Area for the NAA or choline peak to the area for the creatine peak is relatively increased after surgery (NAA/creatine, 1.83; choline/creatine, 1.06) (right graph) compared with the preoperative spectrum (NAA/creatine, 1.56; choline/creatine, 0.86) (left graph).

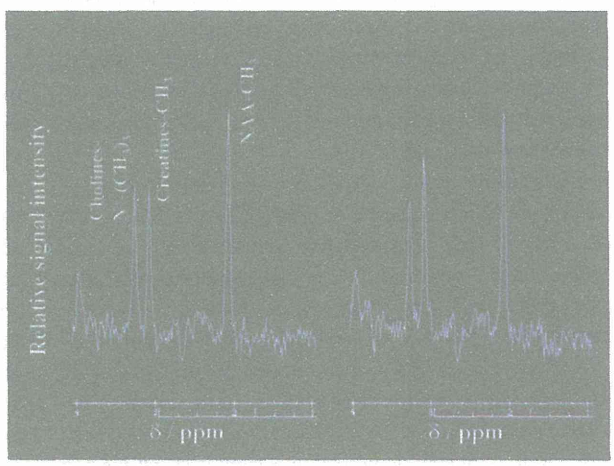

FIG 4. Proton MR spectra obtained by using point-resolved spectroscopy in the region of interest in the cerebral hemisphere ipsilateral to the operative site in a 72-year-old man with impaired cognition after endarterectomy for symptomatic left internal carotid artery stenosis. The area for the NAA or choline peak to the area for the creatine peak is relatively reduced after surgery (NAA/creatine, 1.33; choline/creatine, 0.83) (right graph) compared with the preoperative spectrum (NAA/creatine, 1.57; choline/creatine, 0.99) (left graph).

tio following shunting is related to postoperative cognitive improvement,[19] which is consistent with observations from the present study. Therefore, a reduction in NAA may be reversible, and the level of NAA can recover with cognitive improvement, probably resulting from restoration of brain perfusion following surgery.

A postoperative decrease in Cho/Cr ratios in the ipsilateral cerebral hemisphere was significantly associated with postoperative impairment in cognition. The level of choline in the brain may be associated with membrane synthesis or degeneration in neural tissue.[13] Elevation of the choline signal has been demonstrated in patients with multiple sclerosis,[15] in those with severe vasospasm after subarachnoid hemorrhage,[31] and in patients with acute ischemic stroke.[32] In such pathologic conditions, damage to neural tissue may be ongoing, resulting in an increase in myelin membrane degeneration products and leading to elevation of the choline signal. In contrast, the choline level detected on proton MR spectroscopy is decreased in the ischemic cores and in the surrounding tissue that otherwise appears normal on MR imaging performed from 5 to 30 days after the onset of massive cerebral infarction.[33] In this subacute stage of ischemic stroke, damage to the neural tissue is probably complete, and myelin membrane synthesis and degeneration may be reduced, resulting in a decrease in the choline signal. Cho/Cr ratios correlated positively with scores of neuropsychological testing in the elderly population[18,21] and in patients with preclinical Huntington disease.[34] In the latter, investigators have suggested that a decrease in Cho indicates a reduction of myelin membrane turnover that precedes neuronal death that may be responsible for the neuropsychological deficits.[34]

Thus, a postoperative decrease in the Cho/Cr ratio as well as a postoperative decrease in the NAA/Cr ratio may imply neuronal damage caused by CEA, thereby resulting in postoperative cognitive impairment. On the other hand, the univariate analyses showed that the ΔCho/Cr ratio in the cerebral hemisphere ipsilateral to the operative site was significantly higher in patients with postoperatively improved cognition than in those with postoperatively unchanged or impaired cognition, though the multivariate analysis did not demonstrate a significant difference. Considering the correlation between Cho/Cr ratios and cognitive functioning in the elderly population,[18,21] the postoperative increase in Cho may imply recovery of abnormally reduced myelin membrane turnover, resulting in cognitive improvement after surgery.

The relationship between increases or decreases in cerebral metabolite and cognitive changes following CEA remains poorly defined. A recent study suggested that normalization of cerebral metabolism via improvement in cerebral hemodynamics after CEA may result in cognitive improvement.[9] In contrast, cognitive impairment after CEA may result from various mechanisms.[9] First, to perform CEA, the ICA and common carotid arteries are cross-clamped. There is a transient decrease in perfusion in the ipsilateral middle cerebral artery territory in some patients. When the reduction in hemispheric perfusion is significant enough to damage neuronal tissues, it may cause postoperative impairment of cognitive function accompanied by a reduction in cerebral metabolism. Second, a large percentage of patients exhibit evidence of gaseous and particulate emboli in the middle cerebral artery during CEA. The particulate embolization during surgery may result in decreases in cerebral metabolism and neuropsychological deterioration. Third, cerebral hyperperfusion after CEA is defined as a major increase in ipsilateral cerebral blood flow after surgical repair of carotid stenosis that is well above the metabolic demands of the brain tissue. This phenomenon often manifests with unilateral headache, face and eye pain, seizure, and focal symptoms that occur secondary to cerebral edema or intracerebral hemorrhage. Post-CEA hyperperfusion, even when asymptomatic, also causes postoperative cortical neural damage that results in postoperative cognitive impairment.

The univariate analyses in the present study showed that the ΔNAA/Cr ratio in the cerebral hemisphere contralateral to the operative site was significantly higher in patients with postoperatively improved cognition than in those with postoperatively unchanged or impaired cognition. However, multivariate analysis did not demonstrate the significance of this relationship. In the former patients, improvement in cerebral hemodynamics in the contralateral cerebral hemisphere after CEA may result in postoperative increases in cerebral metabolism. When there is contralateral ICA stenosis or occlusion in addition to ipsilateral ICA stenosis, perfusion in the contralateral cerebral hemisphere is often reduced before surgery and may be increased via collateral circulation from the ipsilateral ICA after surgery. However, the incidence of the contralateral ICA stenosis or occlusion was not different among the 3 subgroups of patients with different cognitive changes after surgery. Another possible mechanism may be related to improvement in brain perfusion in the contralateral anterior cerebral artery territory via the anterior communicating artery from the ipsilateral ICA after surgery when the A1 portion of the contralateral anterior cerebral artery is hypoplastic. However, this possibility was not investigated in the present study.

The present study has several limitations that require discussion. First, area ratios for NAA or choline were expressed as a ratio relative to creatine. The absolute value of each area can be obtained from MR spectroscopy. However, the absolute value includes errors arising from variations of magnetic field homogeneity, and converting to the ratio reduces such errors.[35] Creatine concentration is relatively constant in each region of the brain, even in the context of metabolic disease or rapid fluctuation in energy metabolism.[17,24] Muñoz Maniega et al[33] demonstrated that while creatine concentration was significantly reduced in the ischemic cores, it did not change in surrounding tissue that otherwise appeared normal on MR imaging. Because the present study did not include patients with new postoperative ischemic lesions on MR imaging, postoperative changes of total creatine concentration may minimally affect our results. Second, the cerebral hemisphere ipsilateral to the ICA stenosis often exhibits brain atrophy even when massive cortical infarction is not detected on MR imaging in the cerebral hemisphere.[36] In that situation, the proportion of CSF occupying the region of interest for measurement of cerebral metabolites by using MR spectroscopy is higher, thereby reducing the accuracy of metabolic ratios measured by MR spectroscopy.[36] Finally, a single-voxel region of interest for measurement of metabolites was placed on the section through the centrum semiovale. The value in the single-voxel region of interest does not always reflect the metabolic condition in the whole cerebral hemisphere. Although a topographic map of cerebral metabolism can be obtained by using a multivoxel method, metabolic values acquired from a single voxel may provide more accurate quantification of cerebral metabolic ratios than those acquired from multiple voxels.[11]

CONCLUSIONS

The present study by using 3T proton MR spectroscopy in a relatively large number of patients demonstrated that postoperative changes in cerebral metabolites are associated with changes in cognitive function after CEA. Further investigations by using other modalities, such as oxygen 15 gas or [^{18}F] fluorodeoxyglucose positron-emission tomography, would be of benefit to confirm the relationship between changes in cerebral metabolism and change in cognitive function after CEA.

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ORIGINAL ARTICLE

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Changes in Cognitive Function After Carotid Endarterectomy in Older Patients: Comparison With Younger Patients

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Abstract

Objective and subjective assessments of changes in cognition after carotid endarterectomy (CEA) were compared between older patients (≥76 years old) and younger patients (<76 years old). Patients underwent subjective cognitive assessment by a neurosurgeon and the patient's next of kin, and neuropsychological testing (five parameters) before and after surgery. Of 37 older patients studied, 4 (11%), 28 (75%), and 5 (14%) patients were defined as having subjectively improved, unchanged, and impaired cognition, respectively, following surgery. Differences in test scores (postoperative test score − preoperative test score: Δ score) in all neuropsychological tests were significantly lower in the older patients than in the 213 younger patients. The Δ score was able to statistically differentiate older patients with subjectively improved, unchanged, and impaired cognition after surgery. Receiver operating characteristic analysis showed that the Δ score cut-off point for detecting subjective improvement (upper cut-off point) and impairment (lower cut-off point) in cognition after surgery in older patients was identical to the mean or the mean +0.5 standard deviation (SD) and the mean −1.5 SD or the mean −1 SD, respectively, of the control value obtained from normal subjects. The upper and lower cut-off points were lower and higher, respectively, than those in younger patients. In conclusion, although neuropsychological test scores reflect the subjective assessment of postoperative change in cognition in older patients, the optimal cut-off points for the test scores to detect subjective improvement and impairment in cognition after CEA are different in older patients compared with younger patients.

Key words: carotid endarterectomy, cognition, neuropsychological test, elderly

Introduction

Carotid endarterectomy (CEA) reduces the risk of stroke in selected patients with carotid disease.[4] Numerous studies have investigated changes in cognitive function following CEA using objective neuropsychological testing and found that, while CEA may improve cognitive function,[9,17] cognitive impairment occurs in 10% to 30% of patients following CEA.[7,12,13,20] However, reports defined no clear criteria for determining significant cognitive improvement or impairment after surgery on neuropsychological test scores, because such postoperative changes may, in part, reflect the "practice effect" (an improvement in scores when patients are repeatedly tested).[12,17] In contrast, physicians and/or patients' families often report subjective postoperative improvements or impairments in cognition for patients undergoing CEA; indeed, patients <76 years old who underwent CEA experienced subjective improvement in 11% and impairment of cognition in 11% of cases after surgery.[22] Further, neuropsychological testing can detect subjective improvement and impairment in cognition after surgery if the optimal cut-off points for changes of the test scores are defined.[22]

CEA is an effective means of preventing stroke recurrence even in elderly patients.[3] However, whether cognitive function changes following CEA in such patients remains unclear. Several investigators showed significant improvement in cognitive performance scores after CEA,[1] but others demonstrated no significant differences in scores on cognitive tests before and after surgery.[10] Further, no studies have compared cognitive changes after CEA in

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younger versus older patients.

The present study performed objective and subjective assessments of changes in cognition after CEA in older patients (≥76 years old) and compared the findings with data from younger patients (<76 years old) obtained previously.[22]

Patients and Methods

Of 296 patients who underwent CEA from April 2000 to December 2007,[22] 39 satisfied the following criteria and were prospectively enrolled: age, ≥76 years; ipsilateral severe internal carotid artery (ICA) stenosis (≥70%) on angiography with arterial catheterization; preoperative useful residual function (modified Rankin disability scale 0 or 1); no ipsilateral carotid territory ischemic symptoms or ipsilateral carotid territory ischemic symptoms that had occurred >6 months before presentation to our department (defined as asymptomatic) or ipsilateral carotid territory ischemic symptoms that had occurred between 2 weeks and 6 months before presentation to our department (defined as symptomatic); no further ischemic symptoms during the period between initial evaluation and surgical intervention; no new major neurological deficits on recovery from anesthesia following surgery for CEA; and written informed consent obtained from both the patient and next of kin. A total of 213 patients who were aged <76 years satisfied the above-mentioned criteria (with the exception of age)[22] and served as a group of younger patients. This study was reviewed and approved by the institutional ethics committee of Iwate Medical University.

The same surgeon (K.O.) performed CEA for all patients who were enrolled in the present study. Surgery was performed under general anesthesia and with the use of an operative microscope from the skin incision. Neither intraluminal shunt nor patch grafts were used in these procedures. A bolus of heparin (5000 U) was given prior to ICA clamping.

Cerebral blood flow (CBF) was measured preoperatively and immediately after surgery using iodine-123 N-isopropyl-p-iodoamphetamine single-photon emission tomography (SPECT) as described previously.[19] Based on the CBF values measured using brain perfusion SPECT, post-CEA hyperperfusion was defined as described previously.[19] Diffusion-weighted magnetic resonance (MR) imaging was performed before and within 24 hours after surgery to identify new postoperative ischemic lesions.

Patients visited the attending neurosurgeon (K.O.) in our outpatient clinic within 7 days before surgery, and between 1 and 2 months after surgery. At each visit, the neurosurgeon interviewed the patient for approximately 30 minutes, and at the postoperative visit, the neurosurgeon subjectively assessed whether the patient's cognition was improved, impaired, or unchanged after surgery compared with the patient's preoperative cognition. A neurologist who was unaware of the neurosurgeon's assessment also asked the patient's next of kin whether the patient's cognition was improved, impaired, or unchanged after the surgery compared with the patient's preoperative cognition. In this assessment, the patient's next of kin subjectively determined the postoperative cognitive change. As reported previously,[22] a patient was defined as having subjective improvement or impairment in cognition after surgery when both the neurosurgeon and the patient's next of kin agreed that either postoperative improvement or impairments was present. A patient was defined as having subjectively unchanged cognition after surgery in all other cases.

To objectively assess postoperative changes in cognition, a battery of neuropsychological tests was administered, consisting of the Japanese translation of the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[21] the Japanese translation of the Wechsler Memory Scale (WMS),[14] and the Rey-Osterreith Complex Figure test (Rey test).[16] The WAIS-R generates a verbal and performance intelligence quotient (IQ). The Rey test evaluates copy and recall of a complex figure. Thus, five scores (WAIS-R verbal IQ, WAIS-R performance IQ, WMS, Rey copy, and Rey recall) were used to objectively evaluate cognitive function.[22] In the WAIS-R and WMS, normal control values in subjects aged ≥76 years are not available.[14,21] Thus, normal control values from subjects aged 75 years were used to standardize raw data from patients who were aged ≥76 years. The preoperative and postoperative neuropsychological tests were performed within 7 days after the subjective assessment of cognition, and differences in each neuropsychological test score (postoperative test score − preoperative test score) were calculated and defined as the Δ score. All examinations were administered by a trained neuropsychologist who was unaware of the patient's clinical information.

Forty healthy volunteers (37 men, 3 women; mean age, 60 years; range, 45–70 years) served as controls and underwent the same neuropsychological tests on two separate occasions.[22] The interval between the two tests ranged from 1 to 2 months. Differences in each neuropsychological test score between the two tests (second test score − first test score), were defined as Δ score in controls. In this control group, the Δ score was 3.4 ± 4.5 (mean ± standard deviation [SD]) on the WAIS-R verbal IQ, 4.9 ± 5.0 on the