Adverse effects of pre-existing cerebral small vessel diseases on cognitive improvement after carotid endarterectomy

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Abstract

Background: Although patients with improved cognition after carotid endarterectomy usually exhibit postoperative restoration of cerebral blood flow, less than half of patients with such cerebral blood flow change have postoperatively improved cognition. Cerebral small vessel disease on magnetic resonance imaging is associated with irreversible cognitive impairment.

Aims: The purpose of the present prospective study was to determine whether pre-existing cerebral small vessel disease affects cognitive improvement after carotid endarterectomy

Methods: Brain MR imaging was performed preoperatively, and the number or grade of each cerebral small vessel disease was determined in 80 patients undergoing carotid endarterectomy for ipsilateral internal carotid artery stenosis (70%). The volume of white matter hyperintensities relative to the intracranial volume was also calculated. Brain perfusion single-photon emission computed tomography and neuropsychological testing were performed preoperatively and two months postoperatively. Based on these data, a postoperative increase in cerebral blood flow and postoperative improved cognition, respectively, were determined.

Results: Logistic regression analysis using the sequential backward elimination approach revealed that a postoperative increase in cerebral blood flow (95% confidence interval [CI], 10.74–3730.00; P ¼ 0.0004) and the relative volume of white matter hyperintensities (95% CI, 0.01–0.63; P ¼ 0.0314) were significantly associated with postoperative improved cognition. Although eight of nine patients with postoperative improved cognition exhibited both a relative volume of white matter hyperintensities

0.65% had postoperative improved cognition regardless of any postoperative change in cerebral blood flow.

Conclusion: Pre-existing cerebral white matter hyperintensities on magnetic resonance imaging adversely affect cognitive improvement after carotid endarterectomy.

Key words

Carotid endarterectomy, cognition, cerebral small vessel disease, cerebral white matter hyperintensity, cerebral blood flow

Introduction

In select patients with severe stenosis of the cervical internal carotid artery (ICA), carotid endarterectomy (CEA) can be performed for stroke prophylaxis. Furthermore, cognitive function improves after CEA in approximately 10% of asymptomatic patients as well as symptomatic patients.1–4 This cognitive improvement is reportedly related to postoperative restoration of brain perfusion that was reduced before surgery.1,4 Restoration of perfusion leads to improvement in cerebral metabolism,2 functional recovery of the cortical neurotransmitter system,1 and remyelination of cerebral white matter tracts,3 resulting in cognitive improvement. Although patients with postoperatively improved cognition usually exhibit these changes following restoration of brain perfusion, less than half of patients with postoperative restoration of cerebral blood flow (CBF) show postoperatively improved cognition with such changes.1–4 These findings suggest that other factors in addition to postoperative restoration of CBF may be associated with postoperatively improved cognition. Cerebral small vessel disease (SVD) includes multiple types of abnormalities of the small blood vessels in the brain.5,6 Atherosclerosis often affects the smaller blood vessels that supply the brain, leading to this condition.5,6 Further, cerebral SVD is commonly present in patients with severe atherosclerotic stenosis of the cervical ICA.7,8 Cerebral microbleeds (CMBs), lacunar infarcts (LIs), cerebral white matter hyperintensities (WMHs), and enlarged perivascular spaces (EPVSs) are manifestations of cerebral SVD.5,6 Each of these manifestations is also associated with cognitive decline.9–12 The following research questions are thus raised. When CBF is restored after CEA, does postoperative improvement in cognitive function depend on pre-existing cerebral SVD?

The purpose of the present study was to determine whether pre-existing cerebral SVD affects cognitive improvement after CEA.

Methods

Study Design

The design for this prospective observational study was reviewed and approved by the institutional ethics committee at our institution. We obtained written, informed consent from each patient or the patient's next of kin before study enrollment.

Patients

We enrolled patients who underwent CEA of the carotid bifurcation at our hospital and who met the following inclusion criteria: (1) symptomatic (ischemic episodes that were present 2 weeks before the patient came to our institution) or asymptomatic ipsilateral ICA stenosis 70% as defined by the North American Symptomatic Carotid Endarterectomy Trial that was seen with magnetic resonance (MR) angiography/arterial catheterization; (2) modified Rankin scale score of 0–2, indicating good residual function before surgery; (3) no cortical infarct or presence of infarcts that did not occupy the entire cortical area supplied by the M4 branch of the middle cerebral artery (MCA) in the affected cerebral hemisphere as seen with MR imaging; and (4) absence of prior symptomatic hemorrhage (subarachnoid or intracerebral). Patients who satisfy the above criteria usually undergo CEA rather than carotid artery stenting in our institute. We excluded patients showing new ischemic lesions as seen with MR imaging two weeks postoperatively.

Brain MR imaging, definition of SVD, and measurement of volume of WMHs

T1-weighted imaging, T2-weighted imaging, flow-attenuated inversion recovery (FLAIR), and susceptibilityweighted imaging were performed using a 3T MR imaging scanner (TRILLIUM OVAL; Hitachi Medical Corporation, Tokyo). The last imaging was analytically generated from the magnitude and phase images obtained by the three-dimensional T2*-weighted imaging. All MR imaging was performed within 14 days before surgery. For each patient, the number or grade of CMBs,13,14 LIs,14 WMHs,15 and EPVSs14 as manifestations of cerebral SVD was determined according to the criteria reported previously. CMBs or LIs were determined in deep brain regions such as the basal ganglia, thalamus, brain stem, and cerebellum (defined as deep CMBs [DCMBs] or deep LIs [DLIs], respectively) and in cerebral subcortical regions (defined as lobar CMBs [LCMBs] or lobar LIs [LLIs], respectively).13,14 WMHs were determined in the deep subcortical regions (defined as DSWMHs) and the periventricular regions (defined as PVWMHs) and were graded according to the Fazekas scale.16 When WMHs could not be discriminated from infarcts, the Fazekas scale of WMHs was determined in the cerebral hemisphere contralateral to the surgery side. For each patient, an overall SVD burden score was also calculated as follows: one point each was scored if the number of DCMBs, LCMBs, DLIs, or LLIs was 1; one point each was scored if the Fazekas scale16 of DSWMHs or PVWMHs was 2; one or two points were scored if the number of EPVSs was 11–25 or > 25, respectively.17 The overall SVD burden score thus ranged from 0 (no SVD burden) to 8 (maximal SVD burden). To assess interobserver variability of each item in the

SVD burden score, all MR images were independently reviewed by two experienced neuroradiologists who were blinded to all clinical information about the patient and to the determination of the other neuroradiologist. To determine intraobserver variability, one observer reviewed the same images twice (three months apart).

In addition to the subjective assessment of SVD, the volume of WMHs was quantified as follows. First, FLAIR images were segmented into gray and white matter and cerebrospinal fluid space using SPM12; this method also yielded intensity inhomogeneitycorrected images (IICIs),18,19 which were anatomically normalized to the template space using advanced normalization tools.20 A region of interest (ROI) delineating the middle cerebellar peduncle was applied to the anatomically normalized IICIs to estimate the intensity distribution of normal white matter in each subject. The IICIs in native space were then normalized to their intensities to have an overall mean of 1000 and a standard deviation (SD) of 100 in normal white matter distribution. The intensity normalized IICIs were thresholded by a cut-off of 3.5 SDs to segment WMHs, with search regions limited for WMH mask. Small clusters with 20 voxels or less were eliminated to clean up the segmented WMHs. Finally, LIs showing hyperintensities on FLAIR images were manually excluded, and the WMH volume was calculated by multiplying the voxel size by the slice thickness. The intracranial volume was also calculated using the methods described by Buckner et al.,21 and the volume of WMHs relative to the intracranial volume (%) was calculated.

Brain single-photon emission computed tomography and definition of postoperative

increase in CBF

Brain perfusion single-photon emission computed tomography (SPECT) was performed using N-isopropyl-p-[123I]-iodoamphetamine within seven days after preoperative 3T MR imaging and two months after CEA as described previously.22 For anatomic standardization, SPECT images were transformed into the standard brain template with linear and nonlinear transformation using SPM2 software (FUJIFILM RI Pharma, Tokyo).18 Also using SPM2, 318 constant ROIs were automatically set in the cerebral and cerebellar hemispheres using a threedimensional stereotaxic ROI template.23 ROIs were assessed in nine regions (callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, posterior, and hippocampus) in each hemisphere as determined by the arterial supply. Five (precentral, central, parietal, angular, and temporal) of these nine regions were combined and considered to be the ROI supplied by the MCA. The mean radioactive counts on SPECT images were measured in the MCA ROIs in bilateral cerebral hemispheres. The asymmetry index (AI), which was determined pre- and postoperatively, of the radioactive counts was calculated as follows: 100 (radioactive count in the MCA ROI ipsilateral to CEA radioactive count in the contralateral MCA ROI)/[(radioactive count in the MCA ROI ipsilateral to CEA þ radioactive count in the contralateral MCA ROI)/2]. Postsurgical AI values minus presurgical AI values were defined as the DCBF AI. When DCBF AI in a patient was higher than the mean þ2 SD (8.4) of healthy subjects (obtained in a previous study), the patient was defined as having a postoperative increase in CBF.1

Definition of postoperative improved cognition

Each patient was assessed with the following neuropsychological tests: the Wechsler Adult Intelligence Scale Revised (WAIS-R),24 which measures verbal and performance intelligence quotient (IQ); the Wechsler Memory Scale (WMS), which measures memory quotient (MQ);25 and the Rey–Osterrieth Complex Figure test (Rey test),26 in which patients must copy and recall a complex figure. Thus, cognitive abilities were evaluated according to scores on these five tests (WAIS-R verbal IQ, WAIS-R performance IQ, WMS MQ, Rey copy, and Rey recall). These tests were performed by a trained neuropsychologist who was unaware of the medical data for the patient. These neuropsychological tests (both before and after surgery) were performed within one week of brain perfusion SPECT. We calculated the postsurgical test score minus the presurgical test score for each patient, and improved cognition after surgery was defined according to this difference.27 Control data for these neuropsychological tests were obtained from 40 healthy individuals on two independent occasions.27 In the controls, the difference between the second and first test scores was calculated. In the patients, improved cognition was defined as a test score greater than the mean þ2 SD of the difference calculated for the controls: WAIS-R verbal IQ, 12.4; WAIS-R performance IQ, 14.9; WMS MQ, 16.9; Rey copy, 2.6; Rey recall, 9.9.27 Postoperative improved cognition was defined as a significant increase in the difference in at least one of these five tests.27

Preoperative and intraoperative management

Antiplatelet therapy was given to all patients until the morning of the day of CEA, which was performed under general anesthesia. An intraluminal shunt was implanted if

determined to be necessary from intraoperative monitoring of transcranial cerebral oxygen saturation using near-infrared spectroscopy.28 Before clamping of the ICA, a bolus of heparin (5000 IU) was administered.

Statistical analysis

The required sample size to test for superiority of a postoperative increase in CBF on postoperative improved cognition was determined. The incidence of postoperative improved cognition was estimated to be 38% in patients with a postoperative increase in CBF and 0% in patients without such an increase.1 The ratio of the number of former patients to that of the latter patients in a standard patient population was estimated to be 0.2.1 We calculated that 72 patients would be required for a statistical power of 80% and an a error of 5% to detect a 38% difference in the incidence of postoperative improved cognition. The required sample size was finally determined to be 80. Data are expressed as the mean ± SD. To determine the interobserver and intraobserver agreement of each item in the SVD burden score on MR imaging, the j statistics was calculated using data determined by the two observers. The j values obtained were interpreted as follows: values ≤ 0.40 represented poor agreement, values >0.40 and ≤ 0.65 represented fair agreement, values >0.65 and ≤ 0.75 represented good agreement, and values >0.75 represented excellent agreement. The first MR imaging assessments by the first observer were used for all the following analyses. However, when they did not agree with the MR imaging assessments by the second observer, these disagreements were resolved by consensus between the two reviewers. Changes between values in the first and second studies were evaluated using the

Wilcoxon signed-rank test. The relationship between a parameter of interest and postsurgical improved cognition was assessed using univariate analysis with the Mann–Whitney U test or the v2 test. Logistic regression analysis of factors related to postsurgical improved cognition was performed using the sequential backward elimination approach. When the P value of all remaining variables became < 0.05 was considered statistically significant for all assessments. The cut-off point lying closest to the upper left corner of a receiver operating characteristic (ROC) curve for the relative volume of WMHs to predict postsurgical improved cognition was determined when the relationship between the two was statistically significant.

Results

A total of 88 patients met the inclusion criteria over a 24-month period. Two patients declined to participate in this study, and three others did not undergo 3T MR imaging due to the presence of an implanted device that precluded MR imaging. The remaining 83 patients underwent preoperative 3T MR imaging, brain perfusion SPECT, and neuropsychological testing. Two patients had new ischemic lesions on postoperative MR imaging, and another did not undergo postoperative neuropsychological testing; these three patients were excluded from further analysis. Finally, 80 patients who underwent all study testing were assessed. Interobserver [j ¼ 0.67 (95% CI, 0.60–0.75)] and intraobserver [j ¼ 0.92 (95% CI, 0.89–0.96)] agreements in each item of the SVD burden score were good and excellent, respectively. Table 1 shows the range of the number of each SVD; the numbers of patients with DCMBs, LCMBs, DLIs, or LLIs 1; the numbers of patients with EPVSs ≤ 10, from

11 to 25, and 26; the numbers of patients with the Fazekas scale of DSWMHs or PVWMHs of 0, 1, 2, and 3; and the numbers of patients with an overall SVD burden score of 0, 1, 2, 3, 4, 5, and 6 for all patients studied. The second brain perfusion SPECT was performed 57 to 65 days (60.4 ± 2.5) after surgery. CBF AI was significantly increased after surgery (−0.86 ± 8.49) compared to before surgery (−5.51 ± 8.72) ($P < 0.0001$). DCBF AI ranged from −6.34 to 30.94 (4.65 ± 7.74). Eighteen patients (23%) had a postoperative increase in CBF. Based on pre- and postoperative neuropsychological testing, nine patients (11%) showed postoperative improved cognition. Table 2 shows the results of univariate analyses of factors related to postoperative improved cognition. The Fazekas scales of PVWMHs and DSWMHs and the relative volume of WMHs were significantly lower in patients with postoperative improved cognition than in those without postoperative improved cognition. The incidence of a postoperative increase in CBF was significantly greater in patients with postoperative improved cognition than in those without postoperative improved cognition. No other variables including overall SVD burden score were associated with cognitive improvement after surgery. Logistic regression analysis with inclusion of PVWMHs and DSWMHs and exclusion of the relative volume of WMHs revealed that a postoperative increase in CBF (95% CI, 13.61– 1567.89; P ¼ 0.0073) and Fazekas scale of PVWMHs (95% CI, 0.01–0.42; P ¼ 0.0006) were significantly associated with postoperative improved cognition. Logistic regression analysis with exclusion of PVWMHs and DSWMHs and inclusion of the relative volume of WMHs revealed that a postoperative increase in CBF (95% CI, 10.74–3730.00; P ¼ 0.0004) and the relative volume of WMHs (95% CI, 0.01–0.63; P ¼ 0.0314) were significantly associated with postoperative improved cognition.

Eight (89%) of nine patients with postoperative improved cognition exhibited both a Fazekas scale of PVWMHs $\leq$ 1 and a postoperative increase in CBF; the other exhibited a Fazekas scale of PVWMHs $\leq$ 1 and the absence of a postoperative increase in CBF. In contrast, none of the patients with a Fazekas scale of PVWMHs 2 had postoperative improved cognition regardless of any postoperative change in CBF.

Figure 1 shows the relationships among the relative volume of WMHs, DCBF AI, and postoperative improved cognition. The cut-off point lying closest to the upper left corner of the ROC curve for the relative volume of WMHs to predict postoperative improved cognition was 0.65%. Eight (89%) of nine patients with postoperative improved cognition exhibited both a volume of WMHs <0.65% and a postoperative increase in CBF; the other exhibited a volume of WMHs <0.65% and the absence of a postoperative increase in CBF. In contrast, none of the patients with a volume of WMHs $\geq$ 0.65% had postoperative improved cognition regardless of any postoperative change in CBF. Preoperative MR images and pre- and postoperative brain perfusion SPECT images in a patient without postoperative improved cognition despite the presence of a postoperative increase in CBF are shown in Figure 2.

Discussion

The present study demonstrated that pre-existing WMHs on MR imaging adversely affected cognitive improvement after CEA even in the presence of improved post-procedural CBF.

Changes in cognitive function after CEA have been examined with neuropsychological

tests.27 However, guidelines that establish significant improvements in cognitive ability are not available. Some changes may be due to a ‘‘practice effect’’ in which scores improve with repeated testing.27 Subjective changes in cognition after CEA are sometimes reported by the patient’s family members or doctors.27 A study that used ROC curves demonstrated the optimal cut-off points for an increase in neuropsychological test scores after surgery (including the five tests performed in our current study) that detect subjective improvements in cognitive function after surgery.27 These cut-off points reflected subjectively improved cognitive function with positive- and negative-predictive values that were both greater than 80%.27 Our data analyzed using the same definitions showed postoperative improved cognition in 11% of patients undergoing CEA, which corresponded to a previous finding.27

The present study investigated adverse effects of preexisting cerebral SVD on postoperative improved cognition rather than those of pre-existing massive cortical infarcts (defined as infarcts occupying the entire cortical area supplied by the M4 branch of the MCA) or ischemic lesions due to an intraoperative or postoperative embolism on postoperative improved cognition. Thus, patients with the latter pathologies were excluded from the present study.

In our current study, we observed that 23% of patients showed an increase in CBF after surgery. The incidence of increased CBF was significantly higher in patients with postsurgical improved cognition than in those without cognitive improvement. However, fewer than half of patients with a postsurgical increase in CBF also showed improved cognition. These data also corresponded with previous findings.1

One of the main findings in the present study was that patients with severe or massive WMHs before surgery never have postoperative improved cognition despite a postoperative change in CBF. This finding showed that pre-existing WMHs adversely affect cognitive improvement after CEA and that preoperative MR imaging predicts patients who will not experience cognitive improvement after CEA. The underlying pathology of WMHs is heterogeneous, ranging from mild demyelination to incomplete subcortical infarctions.29 These lesions are associated with cognitive impairment, although the exact mechanisms are not fully understood.30,31 A possible mechanism is thinning of the previously connected cortex.29 Several studies have conducted voxel-based morphometry and showed that WMHs are associated with regional cortical atrophy.32,33 Another possible mechanism is that WMHs may affect the cortex at the network level. The interactions between brain regions are important for efficient cognitive function. A recent network analysis demonstrated that disconnection of networks is associated with WMHs and worsening cognitive function.29 In addition, WMHs located in certain white matter tracts are associated with cortical thickness and network measures in particular cortical areas.29 Patients with severe WMHs may thus have such a disruption in their networks, resulting in no postoperative improvement in cognition despite a postoperative increase in CBF.

The present study also showed that patients with a combination of fewer preoperative WMHs and the presence of a postoperative increase in CBF usually had postoperative improved cognition, suggesting that these two factors are necessary and sufficient conditions for postoperative improved cognition. In patients without network disruption in the brain, restoration of brain perfusion may lead to improvement in cerebral metabolism,2

functional recovery of the cortical neurotransmitter system,1 and remyelination in the cerebral white matter,3 resulting in cognitive improvement.

The present study has serious limitations. First, although a history of the presence or absence of ischemic symptoms was not associated with cognitive improvement after surgery, cognition may spontaneously improve several months after the last ischemic event in symptomatic patients, which may influence the present results. Second, the present study did not include patients who visited our department within <2 weeks of their last ischemic event or those who had massive cortical infarcts, and the results of the present study do not apply to such patients. Third, we did not perform voxel-based morphometry or network analyses. Thus, whether cortical atrophy or networkdisruption specifically inhibited postoperative improvement in cognition in our patients with severe WMHs remains unknown. Lastly, the sample size of the present study is too small to investigate the relationship between each type of SVD abnormality and cognitive change after CEA.

In conclusion, pre-existing WMHs on MR imaging adversely affect cognitive improvement after CEA. Preoperative MR imaging predicts patients who will not develop cognitive improvement after CEA.

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Figure 1. Relationships among the relative volume of white matter hyperintensities (WMHs), D cerebral blood flow (CBF) asymmetry index (AI), and postoperative improved cognition. Closed and open circles denote patients with and without postoperative improved cognition, respectively. The dotted horizontal line denotes the mean þ2 standard deviations for healthy subjects. The dotted vertical line denotes the cut-off point obtained from a receiver operating characteristics curve.

Figure 2. Preoperative magnetic resonance image (left), and pre- (middle) and postoperative (right) brain perfusion singlephoton emission tomography images of a 69-year-old man with left internal carotid artery stenosis and no postoperative improvement in cognition. Grade 3 white matter hyperintensities according to the visual Fazekas scale are observed on the magnetic resonance image. Cerebral blood flow in the left cerebral hemisphere was preoperatively reduced and was restored after surgery compared with the right cerebral hemisphere.

Table 1. Number or grade of each SVD and overall SVD burden score for all patients studied

	DCMBs	LCMBs	DLIs	LLIs	EPVS	DSWMHs	DSWMHs	Overall SVD burden score
Range of	0–8	0–10	0–13	0–12	0–31	–	–	–

number of SVD in each patient								
Number of patients with SVD 1	14 (18%)	5 (6%)	41 (51%)	33 (41%)	–	–	–	–
Number of patients with SVD	–	–	–	–		–	–	–
≤ 10					59 (74%)			
≥ 11 and ≤ 25					18 (22%)			
≥ 26					3 (4%)			
Number of patients with Fazekas scale	–	–	–	–	–			
0						8 (10%)	4 (5%)	
1						41 (51%)	35 (44%)	
2						23 (29%)	23 (29%)	
3						8 (10%)	18 (22%)	
Number of patients with score	–	–	–	–	–	–	–	–

0								12(14%)
1								26 (34%)
2								17 (21%)
3								14 (18%)
4								9 (11%)
5								1 (1%)
6								1 (1%)

SVD: small vessel disease; DCMB: deep cerebral microbleed; LCMB: lobar cerebral microbleed; DLI: deep lacunar infarct; LLI: lobar lacunar infarct; PVWMH: periventricular white matter hyperintensity; DSWMH: deep and subcortical white matter hyperintensity; EPVS: enlarged perivascular space.

Table 2. Univariate analysis of factors related to the postoperative improved cognition.

Variables	Postoperative improved cognition		*P*
	Yes (n=9)	No (n=71)	

Age (years, mean±SD)	69.9 ± 5.5	69.9 ± 5.7	0.9754*
Male sex	9 (100%)	67 (94%)	>0.9999**
Hypertension	9 (100%)	59 (83%)	0.3416**
Diabetes mellitus	3 (33%)	27 (38%)	>0.9999**
Dyslipidemia	8 (89%)	49 (69%)	0.4344**
Symptomatic lesion	8 (89%)	51 (72%)	0.4327**
Bilateral lesions	3 (33%)	13 (18%)	0.3732**
Degree of ICA stenosis (%, mean ± SD)	90.0 ± 9.0	87.7 ± 9.8	0.3869*
Duration of ICA clamping (min, mean ± SD)	37.7 ± 5.3	35.0 ± 6.2	0.2139*
Use of intraluminal shunt	0 (0%)	3 (4%)	0.9999**
DCMB (number, mean ± SD)	0.1 ± 0.3	0.4 ± 1.4	0.5570*
LCMB (number, mean ± SD)	0.0 ± 0.0	0.2 ± 1.2	0.4140*
DLI (number, mean ± SD)	1.9 ± 3.0	1.4 ± 2.4	0.7005*
LLI (number, mean ± SD)	0.3 ± 0.5	1.1 ± 2.2	0.3808*
Fazekas scales of PVWMH (mean ± SD)	1.0 ± 0.0	1.8 ± 0.9	0.0069*
Fazekas scales of DSWMH (mean ± SD)	0.9 ± 0.3	1.5 ± 0.8	0.0334*
EPVS (number, mean ± SD)	6.4 ± 3.6	8.3 ± 7.9	0.9635*
Overall SVD burden score (mean ± SD)	1.1 ± 0.9	2.0 ± 1.4	0.0731*
Relative volume of WMHs (%, mean ± SD)	0.46 ± 0.16	1.15 ± 0.89	0.0060*
Postoperative increase in CBF	8 (89%)	10 (14%)	<0.0001**

SD: standard deviation; ICA: internal carotid artery; DCMB: deep cerebral microbleed; LCMB: lobar cerebral microbleed; DLI: deep lacunar infarct; LLI: lobar lacunar infarct; PVWMH: periventricular white matter hyperintensity; DSWMH: deep and subcortical white matter hyperintensity; EPVS: enlarged perivascular space; CBF: cerebral blood flow;

SVD: small vessel disease. *Mann-Whitney U test; ** χ 2 test.

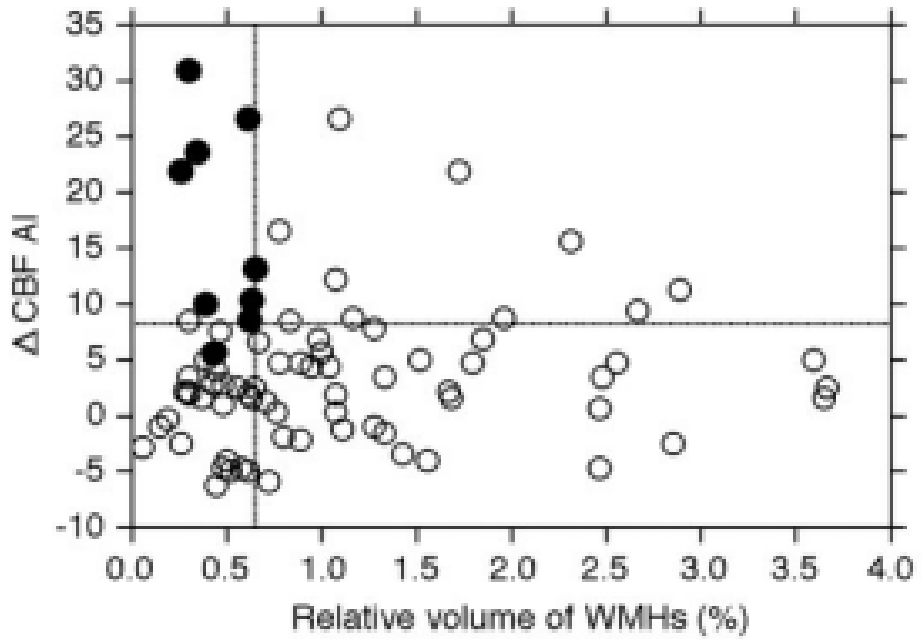
35
30
25
20
15
10
5
0
-5
-10
ΔCBF AI
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Relative volume of WMHs (%)

Figure.1

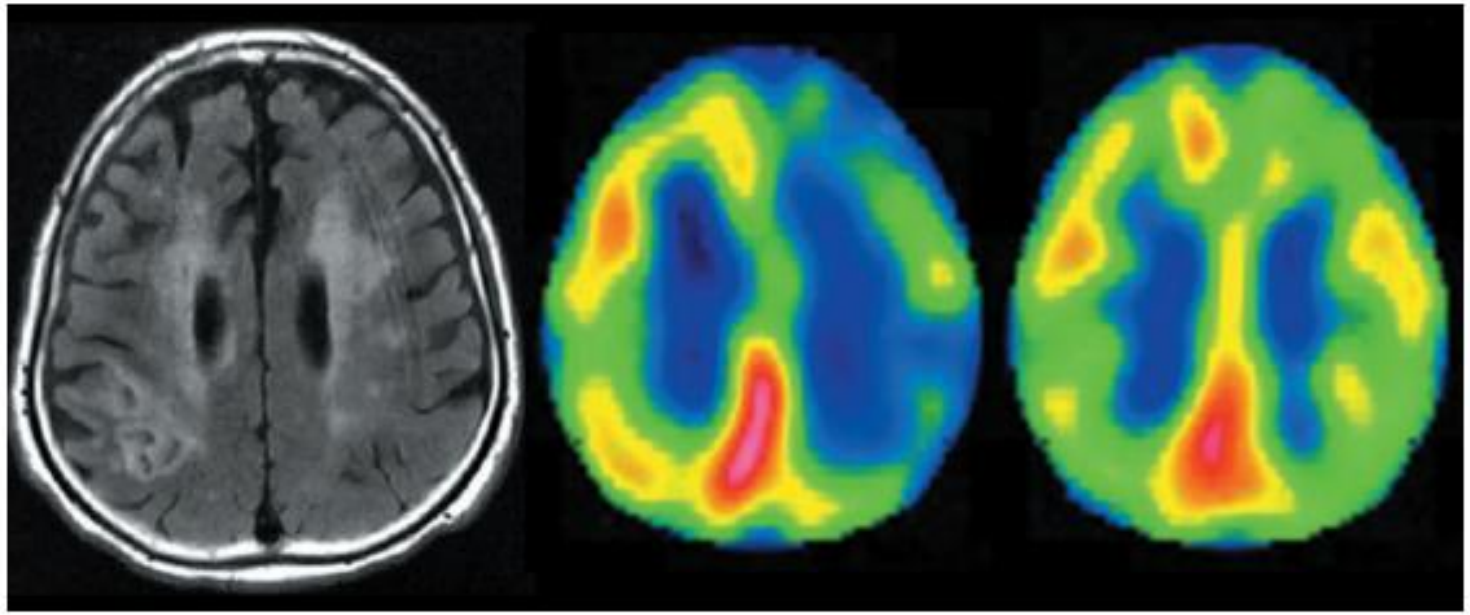

Figure.2