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Long-term effects of white matter changes on the risk of stroke recurrence after carotid artery stenting in patients with symptomatic carotid artery stenosis

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ABSTRACT

Introduction: Cerebral white matter changes (WMC) are associated with increased 30-day perioperative risk of stroke in patients undergoing carotid artery stenting (CAS). However, there is no data showing their impact on postoperative long-term stroke recurrence or survival. It remains unknown whether this effect is independent of classic cardiovascular risk factors or not. We tried to assess the effects of WMC on long-term stroke recurrence after CAS in patients with symptomatic carotid stenosis.
Methods: A database of patients with symptomatic carotid stenosis who had undergone CAS was sampled in a single Chinese medical center from 2007 to 2014. Copies of baseline brain imaging were analyzed by two investigators to evaluate the severity of WMC. We analyzed the association between WMC and stroke recurrence after CAS by reviewing case histories and conducting telephone interviews, with a mean follow-up time of 28 months.
Results: 107 patients with an average age of 66 years fulfilled the inclusion criteria, of which 70 were examined with CT and the remainder by MRI. In our cohort, 91.6% of the participants were male. There were 29 patients with diffuse WMC. In univariate analysis, patients with diffuse WMC had more contralateral occlusion than those with non-diffuse WMC. In patients with diffuse WMC, more stroke recurrences were observed compared with those with non-diffuse WMC (hazard ratio [HR] 3.516; 95% CI 1.176, 10.510, $P = 0.024$).
Conclusions: In patients with symptomatic carotid artery stenosis, diffuse WMC were a risk factor for stroke recurrences after CAS. Larger studies are warranted to confirm this finding and explore the potential clinical impact of WMC so as to better determine treatment strategies for patients with symptomatic carotid artery stenosis.

1. Introduction

White matter changes (WMC), also known as leukoaraiosis, are a common finding on cerebral CT and MRI scans [1–3]. Leukoaraiosis was first proposed by Hachinski et al. to describe the presence of patchy diffuse changes in the periventricular cerebral white matter [4]. It has been reported that the prevalence of white matter lesions is up to 44% on CT and up to 100% on MRI in patients with stroke [5,6].

WMC are associated with a higher perioperative risk of stroke or mortality and long-term stroke recurrence in patients undergoing carotid endarterectomy [7,8]. WMC are also correlated with a higher peri-interventional risk of stroke in patients undergoing CAS. In the International Carotid Stenting Study (ICSS), 536 patients undergoing CAS had baseline imaging available. Those with an Age-Related White Matter Changes (ARWMC) score of 7 or more had an increased risk of stroke than those with a score of <7 [9].

At present, WMC are not evaluated before CAS. Neither is there any data showing their effects on postoperative long-term survival. The primary aim of this study was to evaluate the effects of WMC on the risk of long-term stroke recurrence in a group of patients undergoing CAS for symptomatic carotid artery stenosis.

2. Methods

2.1. Database

Detailed clinical information was obtained from Huashan Hospital, an affiliate of Fudan University, for patients who underwent CAS between January 2007 and December 2014. Inclusion criteria: 1. Experienced retinal or hemisphere ischemic event within 6 months before surgery; 2. Ultrasound/computed tomographic angiography (CTA)/

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Table 1
Demographic and clinical characteristic of patients.

Characteristics	Total ($n = 107$)		WMC < 3 ($n = 78$)		WMC = 3 ($n = 29$)		P
Males, *N* (%)	98	91.60%	71	91.00%	27	93.10%	1
Age, Med years (IQR)	65	(58.73)	65	(57.73)	66	(59.69)	0.93
Most recent ipsilateral event							
Amaurosis fugax, *N* (%)	3	2.80%	3	3.80%	0	0.00%	0.56
TIA, *N* (%)	35	32.70%	26	33.30%	9	31.00%	0.82
Ischemic hemispheric stroke, *N* (%)	78	72.90%	55	70.50%	23	79.30%	0.36
Pervious stroke, *N* (%)	16	15.00%	11	14.10%	5	17.20%	0.69
Diabetes, *N* (%)	29	27.10%	18	23.10%	11	37.90%	0.12
Hypertension, *N* (%)	77	72.00%	55	70.50%	22	75.90%	0.58
CHD, *N* (%)	14	13.10%	9	11.50%	5	17.20%	0.44
PAD, *N* (%)	7	6.50%	7	9.00%	0	0.00%	0.19
History of cancer, *N* (%)	5	4.70%	4	5.10%	1	3.40%	1
CRD, *N* (%)	3	2.80%	2	2.60%	1	3.40%	1
Dyslipidemia, *N* (%)	71	66.40%	53	67.90%	18	62.10%	0.65
BMI Med (IQR)	23.72	(21.22, 25.99)	23.72	(21, 26.04)	23.9	(21.53, 25.95)	0.81
Currently smoking, *N* (%)	48	44.90%	39	50.00%	9	31.03%	0.09

Abbreviations: WMC: white matter changes; BMI: basic metabolic index; CHD: coronary heart disease; CRD: chronic renal disease; IQR: interquartile range; PAD: peripheral arterial disease; TIA: transient ischemia attack.

magnetic resonance angiography (MRA) diagnosed stenosis of extracranial carotid artery with digital subtraction angiography (DSA) confirmed (defined by a luminal narrowing of ≥50% according to the measurement of degree of stenosis used in the North American Symptomatic Carotid Endarterectomy Trial [10]); 3. Pre-interventional cerebral CT/MRI was available for assessment of WMC.

There were 134 patients with symptomatic carotid artery stenosis that underwent CAS during this time period. Among them, 14 cases were excluded that had carotid artery stenosis <50% in DSA assessment and 13 patients were excluded for not having any pre-operational cerebral CT or MRI images available; 107 patients fulfilled the inclusion criteria. Demographic characteristics (including age and sex), comorbidities (including history of hypertension, diabetes, coronary heart disease, and peripheral artery disease), the degree of carotid stenosis and lesion characteristics (including lesion ulceration, contralateral stenosis, contralateral occlusion, and so on) were recorded.

2.2. Definition

Stroke was defined as an acute disturbance of focal neurological function with symptoms lasting >24 h. Cardiovascular risk factors obtained from medical record were determined based on previous diagnosis and current medication as follows: diabetes (diagnosis or taken insulin or oral diabetes medication), hypertension (diagnosis or taken hypertension medication), coronary heart disease (CHD; diagnosis of angina pectoris, myocardial infarction, undergone percutaneous coronary intervention or coronary artery bypass grafting), peripheral arterial disease (PAD; diagnosis or undergone peripheral vascular intervention or amputation) and dyslipidemia (diagnosis). Smoking was defined as currently smoking.

Table 3
Clinical outcomes of patients.

Clinical outcome	Patients completed follow-up (cases) ($n = 99$)	Non-diffuse WMC (cases) ($n = 70$)	Diffuse WMC (cases) ($n = 29$)
Hemorrhagic stroke	3[a] (2 cases dead)	1	2
Ischemic stroke	11[a] (1 case dead)	6	5
Died of renal failure	1[a]	1	0

[a] Among all 15 events, 3 ischemic strokes and 2 hemorrhagic strokes occurred within 30 days after CAS.

2.3. Radiological assessment

Cerebral images of CT or MRI were analyzed by two neurologic doctors blinded to the clinical outcome. Images were analyzed according to the Wahlund criteria [11]. In brief, in the cerebral hemispheres and the brainstem, WMC were identified as poorly defined hyperintense lesions on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI images, hypodense lesions on CT, with a diameter of 5 mm or larger. A 4-point scale was defined as follows: "0" for no lesions (including symmetrical, well-defined caps or bands); "1" for focal lesions; "2" for beginning confluence of lesions; "3" for diffuse involvement of the entire region, with or without involvement of U fibres. Patients with WMC were categorized according to the greatest extent of WMC in different cerebral regions of the frontal area, the temporal area, the parieto-occipital area, the infratentorial area, and the basal ganglia. WMC were analyzed by CT in 70 patients while by MRI in 37 patients. Kappa value for interobserver agreement was 0.592 for CT and 0.803 for MRI.

2.4. Follow-up

Patients were asked to come back for an out-patient appointment one month after the surgery and some of them underwent DSA assessment of the cerebral vascular six months after the surgery. Telephone interviews were carried out in July 2010, March 2014 and February 2015, covering specific time, symptoms, imaging and treatment status of each event that the patient had. Long-term survival data on the status of the patients (recurrent stroke or not) and mortality were obtained by detailed telephone interviews and case reviews. Primary end point was recurrent stroke after surgery. Secondary end point was recurrent stroke and mortality of any cause after surgery.

Table 2
Lesion characteristic of patients.

	Total ($n = 107$)		WMC < 3 ($n = 78$)		WMC = 3 $N = 29$		P
IL stenosis ≥ 70%, *N* (%)	91	85.00%	66	84.60%	25	86.20%	1
Left ICA stent, *N* (%)	57	57.00%	42	58.30%	15	53.60%	0.67
Lesion ulceration, *N* (%)	27	25.20%	19	24.40%	8	27.60%	0.73
CL carotid stenosis, *N* (%)	35	32.70%	26	33.30%	9	31%	0.822
CL carotid occlusion, *N* (%)	16	15.00%	7	9%	9	31%	0.004
Vertebral artery stenosis, *N* (%)	52	48.60%	37	47.40%	15	51.70%	0.693

Abbreviations: WMC: white matter changes; CL: contralateral; ICA: internal carotid artery; IL: ipsilateral.