Original Paper

The Role of White Matter Damage in the Risk of Periprocedural Diffusion-Weighted Lesions after Carotid Artery Stenting

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Carotid artery stenting · Diffusion-weighted images · White matter hyperintensities

Abstract
Background: White matter hyperintensities (WMH) are a common finding in aged individuals affected by carotid artery disease and are a risk factor for first-ever and recurrent stroke. We investigated if white matter damage increases the risk of brain microembolism during carotid artery stenting (CAS), as evaluated by the appearance of new areas of restricted diffusion on diffusion-weighted images (DWI). *Methods:* We evaluated 47 patients with severe internal carotid artery (ICA) stenosis undergoing CAS, comparing preprocedural clinical, ultrasound and radiological characteristics. WMH volume was computed on FLAIR images before CAS. After CAS, the DWI scan was looked over for areas of restricted diffusion (DWI lesions). A first univariate analysis was adopted to compare groups according to the occurrence of DWI lesions. Then, the variable DWI lesion was modelled by means of a logistic regression model. *Results:* Seventeen patients developed at least 1 DWI lesion after CAS. Compared with non-DWI, DWI patients were more commonly treated in the left ICA ($p = 0.007$) and had a more severe WMH damage ($p = 0.027$). Indeed, the risk of a DWI lesion was higher in left versus right stenosis (OR = 9.0, 95% CI 1.9–42.7, $p = 0.005$) and increased for each log-unit of WMH lesion load (OR = 7.05, 95% CI 1.07–46.49, $p = 0.042$). A WMH lesion load of at least 5.25 cm^3

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had a 50% probability of occurrence of a new DWI lesion. **Conclusions:** Treated side and pre-existing white matter damage are risk conditions for brain microembolism during CAS. This should be taken into account to optimize severe carotid artery disease management.

Introduction

Carotid artery stenting (CAS) is a procedure associated with high risk of brain microembolism, usually detected as areas of restricted diffusion on magnetic resonance (MR) diffusion-weighted images (DWI). Although most CAS-related DWI lesions do not cause an obvious neurological deficit, they are demonstrated to impact cognitive function [1] and may represent a surrogate parameter for optimizing diagnostic and therapeutic vascular procedures [2].

Advanced age, plaque characteristics and procedures without emboli protection devices have been advocated as risk factors for new DWI lesions after CAS, even though with conflicting results [3–9].

Brain white matter hyperintensities (WMH) are a common finding in aged individuals affected by carotid artery disease [10]. Although their pathogenesis is largely unknown, a hemodynamic contribution has been supposed [11, 12]. Different studies have shown that a reduced basal cerebral blood flow [13] as well as a poor cerebrovascular response to acetazolamide or hypercapnia are related to white matter changes [14–16].

Moreover, WMH areas present an impaired hemodynamic status, making these areas more likely to be exposed to transient ischemia, which may induce myelin rarefaction [17]. Furthermore, WMH are a recognized risk factor for first-ever and recurrent stroke in population-based studies [18].

We hypothesized that patients with a severe basal WMH lesion load could be more prone to develop DWI lesions during a procedure at high risk for distal embolization, such as CAS. To test this hypothesis, we investigated baseline clinical and radiological characteristics affecting the occurrence of periprocedural DWI lesions in our cohort of patients treated with CAS for severe internal carotid artery disease.

Methods

We retrospectively evaluated 47 patients (mean age 73 years, SD 8; 14 female) with severe (i.e., greater than 70%) carotid artery stenosis, who underwent carotid angioplasty with stent placement at the Interventional Radiology Unit of our institutions from January 2007 to February 2013. Patient enrollment, and clinical, ultrasound and MR evaluations were performed as already described [1].

In summary, plaque characteristics and degree of stenosis were evaluated by ultrasound of neck vessels and confirmed by computed tomographic angiography. Intracranial vessels were examined with transcranial color-coded sonography and MR angiography to exclude significant stenosis of the large intracranial arteries.

All patients underwent electrocardiography and cardiological and neurological examination on admission. Brain MR imaging was performed the day before CAS. No patient had possible or probable embolizing cardiopathy. The day after the procedure, clinical assessment, brain MR imaging, and color-coded duplex sonography of the neck vessels were repeated. In addition, all patients underwent continuous electrocardiographic monitoring in the first 48 h following CAS to detect possible new-onset arrhythmias.

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Therapy with ASA 100 mg plus clopidogrel 75 mg as tablets once a day was initiated at least 5 days before CAS in all patients. Clopidogrel was continued for 6 months after CAS and ASA was administered indefinitely. Each patient received the best medical therapy to control vascular risk factors. The institutional review committee approved the study. All the patients gave their informed written consent.

Stent Placement

Every CAS procedure in the present study was performed under local anesthesia in a dedicated operating room equipped for endovascular procedures by the same 2 experienced radiologists. A femoral access was used to introduce a guidewire up to the origin of the internal carotid artery (ICA). Carotid and cerebral angiography was then performed to confirm the level and the degree of arterial narrowing. The guidewire was then manipulated across the stenosis and a balloon was passed over the device to lie across the stenosis, where it was inflated manually. Thereafter a deployment of the stent into the area of narrowing was done. At the end of the procedure, an angiography was performed to assess the result. Either distal or proximal cerebral protection devices were used.

DWI Lesions and WMH Assessment

MR imaging analysis was conducted by an investigator blinded to clinical patients' data (D.L.). As previously described [1], MR imaging was performed with an Achieva 1.5-T scanner (Philips Medical Systems, Best, the Netherlands) and an 8-channel head phased-array coil with parallel imaging capabilities (SENSE). The following brain MR sequences were collected before and after CAS: axial plane T1-weighted spin echo (TR = 550, TE = 15, slice thickness = 3 mm, interslice gap = 0), FLAIR (TR = 8,000, TE = 125, TI = 2,500, slice thickness = 3 mm, interslice gap = 0), and DWI (TR = 3,220, TE = 88, b value = 1,000, slice thickness = 5 mm, interslice gap = 1 mm) with apparent diffusion coefficient.

Total WMH volume was computed on FLAIR axial images before CAS, after having segmented lesional regions of interest through a semi-automated local thresholding approach (Osirix® software V.3.9.4) [19]. After CAS, the DWI scan was looked over for areas of restricted diffusion (DWI lesions), which were classified according to anatomical localization and side of the treated artery.

Statistical Analysis

WMH distributions were not gaussian (Shapiro-Wilks, $p < 0.001$) and markedly improved the fit after a logarithmic transformation (ratio skewness/SE[skewness] decreased from 3.7 [$p < 0.001$] to 1.1 [$p = 0.28$]). A first analysis including baseline parameters was adopted to compare groups based on the occurrence of postprocedural DWI lesion and served as the basis for a multivariate logistic regression model. Continuous variables were compared using the Mann-Whitney U test or the Student t test, as appropriate. The distributions of the categorical variable were compared using the χ^2 test.

The number of DWI lesions after CAS was put in relation to potential covariates assuming a negative binomial distribution. The variable DWI lesion was also dichotomized (0 = no DWI lesion; 1 = at least 1 DWI lesion) and modelled by means of a logistic regression model. Since the number of patients in the smaller category (i.e., occurrence of at least 1 DWI lesion) was 17, our sample was not large enough to reliably assess the effect of several variables. Thus, we entered in the multivariate model only the variables that showed a significant univariate association with the outcome. Antithrombotic drugs were not included in the multivariate analysis as we prescribed both ASA and clopidogrel to all patients. Data analysis was performed with SPSS® (version 19) for Windows.

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Table 1. Comparison of clinical, ultrasound and MR imaging data between DWI and non-DWI groups

Characteristics	All (n = 47)	DWI– (n = 30)	DWI+ (n = 17)	p value
Clinical data				
Age, years (SD)	73 (8)	75 (7.2)	72 (8.3)	0.248
Gender (female), n (%)	14 (30)	10 (33)	4 (24)	0.480
Hypertension, n (%)	39 (83)	25 (83)	14 (82)	0.932
Diabetes, n (%)	20 (43)	11 (37)	9 (53)	0.278
Hypercholesterolemia, n (%)	37 (79)	26 (87)	11 (65)	0.077
Smoking habit, n (%)	18 (38)	11 (37)	7 (41)	0.760
Ipsilateral previous stroke/TIA[a], n (%)	11 (23)	5 (17)	6 (35)	0.147
Statin therapy, n (%)	29 (62)	20 (67)	9 (53)	0.352
Ultrasound and procedure-related findings				
Degree of stenosis, % (SD)	77.9 (7.9)	78.2 (8.3)	77.4 (7.5)	0.739
Side of stenosis (left), n (%)	21 (45)	9 (30)	12 (71)	**0.007**
Ulcerated plaque, n (%)	8 (17)	7 (23)	1 (5.8)	0.126
Embolic protection (distal), n (%)	43 (91)	26 (60)	17 (39)	0.115
MR imaging analysis				
WMH, cm^3 (SD)	3.9 (4.8)	2.4 (3.2)	6.3 (6.0)	**0.027**[b]

TIA, transient ischemic attack. Figures in bold are significant.
[a] More than 6 months before procedure. [b] t test applied after log-transformation.

Results

Table 1 displays preprocedural clinical characteristics, ultrasound, MR imaging and procedure-related data of the patients enrolled and a comparison between the DWI-positive (DWI+) and DWI-negative (DWI–) groups.

Preprocedural DWI were negative in all patients. All patients had a complete recanalization after the procedure. No major complications were observed either during the intervention or during the follow-up period. One patient reported transient (lasting less than 2 h) left upper limb weakness early after CAS and reported a new DWI lesion on the right precentral gyrus. No other patient presented symptoms suggestive of stroke. Seventeen (36%) out of 47 patients developed at least 1 new DWI lesion after CAS (DWI+ group), without persistent clinical deterioration (Fig. 1). In the DWI+ group, we found a total of 71 new lesions. Fifty-seven (80%) were ipsilateral to the treated artery and 14 were contralateral. Forty DWI lesions (56%) were located in the frontal lobe, 5 (7%) in temporal, 12 (16%) in parietal, 7 (10%) in occipital, and 7 (10%) in basal nuclei. Eight (17%) patients had an ulcerated carotid plaque and distal embolic protection was adopted in 91% of cases (43 patients).

DWI+ patients were more commonly treated in the left ICA compared with DWI– patients ($p = 0.007$). Moreover, DWI + patients had a more severe preprocedural WMH lesion load ($p = 0.027$). No differences were found with respect to clinical data, plaque ulceration or procedure-related findings ($p > 0.05$). History of ipsilateral stroke or transient ischemic attack did not affect the outcome.

When both laterality of ICA and WMH lesion load had been entered in the logistic model, the occurrence of at least 1 new DWI lesion was confirmed related to both variables. The risk of DWI lesions was higher in the left- versus right-side stenosis (OR = 9.0, 95% CI 1.9–42.7, $p = 0.005$) and increased for each log unit of WMH lesion load (OR = 7.05, 95% CI 1.07–46.49, $p = 0.042$). Regardless of the side of the stenosis, we observed that a patient with a WMH lesion load of 5.25 cm^3 has a 50% probability of having new DWI lesions after CAS. It should

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Table 2. Stepwise logistic regression analysis with postprocedural DWI lesion occurrence as dependent variable

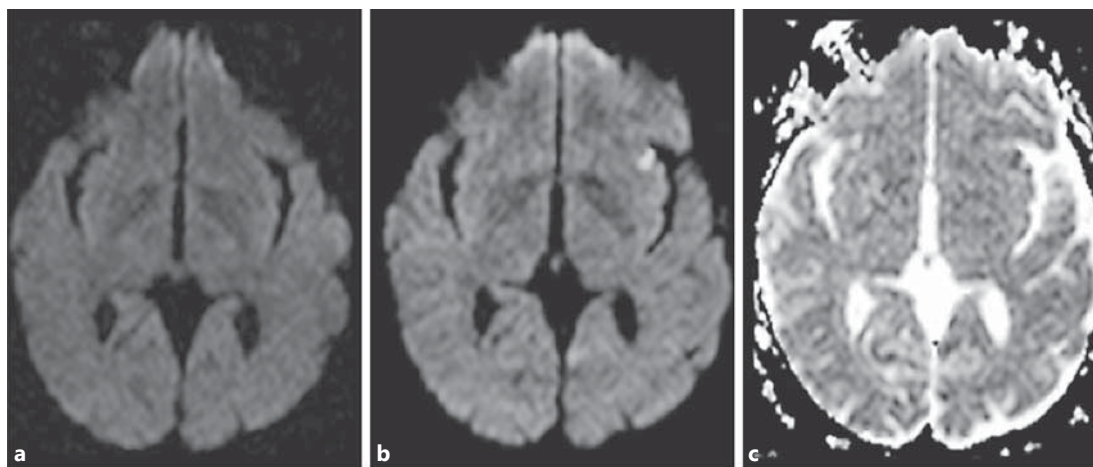| Independent variable	OR	CI	p
Age	1.15	0.99–1.33	0.054
Left-side stenosis	17.12	2.070–141.64	0.008
WMH log	8.97	1.08–74.44	0.042

Fig. 1. Example of an MR imaging study. **a** Preprocedural DWI scan, negative for DWI restriction areas. **b** Postprocedural DWI scan, showing left insular DWI restriction. **c** Postprocedural apparent diffusion coefficient map, confirming a new ischemic lesion on the left insula.

be noted that when age was entered as a "forced" term to remove the plausible aging effect, the effects of side and WMH remained similar (Table 2).

Discussion

In the present study, we retrospectively investigated which factors were most related to the DWI lesions that occurred during the CAS procedure in patients with ICA severe stenosis. Our analysis showed that the treated side (with left > right) and preexisting white matter damage severity were the most relevant risk conditions, also after age correction.

Distal embolization during carotid endovascular procedures could theoretically be related entirely to mechanical factors, i.e., the shear stress applied to the atheroma during balloon inflation or stent deployment, inducing plaque fragmentation and debris migration from the treated artery, or from the aortic arch or common carotid arteries before stent placement. According to this hypothesis, the anatomical features of vessels and plaque morphology should be the main determinants of the risk of periprocedural stroke or DWI-restricted lesions after CAS. Indeed, this is not fully confirmed by literature data.

Plaque length, plaque morphology, ICA angulation, and external or common carotid atheroma have recently been evaluated in an International Carotid Stenting Study (ICSS) substudy and were found not to influence the number of postprocedure DWI lesions in a large cohort of patients [20]. Other studies reported conflicting evidence about plaque morphology [8, 9] as well as about the usefulness of distal protection devices [4–7]. Left-side stenosis has been documented to be an increased risk of distal embolization in 2 previous studies [20, 21], maybe due to a more difficult access to the common carotid artery on this side.

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Hence, to the best of actual evidence, brain vessel anatomy or technical aspects of endovascular procedures are not enough to completely explain what happens in CAS patients. Even if some of the actual uncertainty may be ascribed to inadequate patient sample or underpowered studies, the evidence of a role of preexisting white matter damage underlined by the present study also opens new interesting perspectives.

The reason why a preexisting brain damage may influence the clinical or subclinical outcome of a reasonably safe procedure, independently of age effect, could be ascribed to several pathogenetic mechanisms.

WMH are demonstrated to be more common and extensive in patients with symptomatic cerebrovascular disease [22]. A cerebral hemodynamic impairment has been found in areas of white matter changes, if compared with areas of normal-appearing white matter [17]. However, a global reduced cerebrovascular reactivity has been correlated with the severity of periventricular WMH [15–23]. Globally impaired cerebral hemodynamics may per se cause hypoperfusion of certain brain areas in the basal condition and a reduced emboli washout during a triggering event [24]. This observation could partially explain why DWI-restricted lesions were found not only on the side of the treated artery, which could be directly related to the migration on a small embolus during the endovascular procedure, but also on the contralateral hemisphere and in posterior vascular territories [25].

Findings from an ICSS substudy showed that CAS was associated with a higher risk of ischemic stroke compared with carotid endarterectomy in patients with more extensive age-corrected white matter lesions on brain MR imaging [26]. Our results are in accordance with those of Elderle et al. [26], extending their significance also to apparently asymptomatic ischemic brain lesions.

According to our results and to ICSS substudy findings, we can speculate that patients with a more extensive brain white matter damage have globally compromised cerebral hemodynamics, and for this reason are more prone to develop new ischemic brain lesions, clinically silent or symptomatic, when their unstable balance is upset by a triggering external event.

Since in the general population the prevalence of WMH is strictly associated with age, ranging from 11 to 21% in most octogenarians [27–29], we entered the term "age" in the multivariate model, obtaining similar results.

Current guidelines for the prevention of stroke state that CAS is a reasonable intervention alternative to carotid endarterectomy in patients with severe carotid artery diseases [30–32]. However, in certain clinical settings, such as in the elderly, or in case of arterial anatomy inadequate for endovascular intervention, CAS has been related to an increased risk of periprocedural complications (i.e., stroke, myocardial infarction, or death) and to a long-term risk of ipsilateral stroke if compared to carotid endarterectomy [33]. Moreover, its effectiveness compared with actual best medical therapy is still object of investigation [34].

In this complex scenario, the present study outlines a new issue to ponder about for the best patient management.

Study Limitations

This study has some important limitations. First of all, the small number of patients in the DWI+ group allowed us to assess the effect of only few variables on the final outcome. Moreover, an evaluation of cerebral vasomotor reactivity would have been helpful to test the hypothesis raised from our results; unfortunately, we were not able to perform it in most enrolled patients. Cerebral hemodynamics evaluation should be performed in future similar studies. Finally, our analysis is retrospective and our findings need to be confirmed by a larger prospective clinical study.

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Disclosure Statement

The authors declare that there are no conflicts of interest.

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