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Brain diffusion changes in unilateral carotid artery stenosis with non-shunt endarterectomy: Correlation with white matter lesions

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ABSTRACT

Objective: Carotid stenosis is associated with hemodynamic cerebral ischemia. Diffusion-weighted MR imaging allows for the assessment of changes related to alterations in tissue integrity. The aim of this study was to investigate (a) whether white matter lesions (WML) and apparent diffusion coefficient (ADC) values differ between ipsilateral and contralateral hemispheres, (b) whether ADC values are related to WMLs and common vascular risk factors, and (c) whether ADC values differ after carotid endarterectomy (CEA) without a shunt in patients with unilateral internal carotid artery stenosis (ICAS).
Methods: Twenty-five patients (16 men, 9 women; mean age of 68 years) with unilateral ICAS ($\geq$70% carotid stenosis) were assessed with brain MRI before and after CEA, prospectively. Two experienced radiologists scored the WMLs. Bilateral ADC values in anterior and posterior periventricular WM, occipital WM, and thalamus were evaluated on preoperative and postoperative MRI. Differences in ADC values and WML scores between the two hemispheres were assessed and associations between ADC values, WML scores, and explanatory variables (e.g., age, sex, vascular risk factors) were analyzed.
Results: WMLs were significantly greater and ADC values were elevated in the ipsilateral cerebral WM. After CEA, ADC values rapidly decreased but remained higher than within the contralateral hemisphere. Ipsilateral hemispheric ADC values were associated with basal ganglia WMLs. No association between ADC values and vascular risk factors was found.
Conclusion: ICAS is associated with increased diffusion in normal-appearing WM in comparison to more prominent chronic ischemic lesions. CEA has a partial effect on diffusion. These cerebral changes may be related to chronic low-grade ischemic damage that is induced by ICAS.

1. Introduction

Carotid artery stenosis (CAS) is related to an increased risk of stroke and more prominent chronic ischemic lesions [1,2]. In several randomized clinical trials, carotid endarterectomy (CEA) has been proven to be effective in decreasing the risk of stroke [3].

White matter lesions (WMLs), which are also termed “leukoaraiosis,” are common radiological findings of uncertain pathogenesis that are frequently observed in the periventricular white matter as bilateral diffuse or patchy hyperintensities on T2-weighted magnetic resonance imaging (MRI) [4]. Epidemiological studies demonstrate an increasing frequency of WMLs with advancing age [5]. WMLs have been investigated in numerous studies as potential markers of vascular disease [6–8]. Furthermore, it has been postulated that tissue damage associated with white matter diseases, such as multiple sclerosis, may extend beyond the areas of visible signal abnormalities within routine MRI [9].

Diffusion-weighted MR imaging (DWI) depends on the random diffusion of water molecules within cellular and extracellular tissue compartments [10]. The apparent diffusion coefficient (ADC), a measure of in vivo diffusion at the cellular level, is the net diffusion of water molecules. DWI allows for the assessment of changes associated with alterations in tissue integrity. Thus, they can be useful in quantifying the extent of tissue damage both within and even beyond areas of apparent signal abnormality [9–11]. DWI has been proven to be an essential technique for the detection and differentiation of acute stroke in the early phase, and has also been applied in different phases, of brain ischemia, as well as various

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clinical conditions that are continuously expanding [4,12]. Furthermore, ADC elevation in normal-appearing WM (NAWM) has been reported in patients with a variety of cerebrovascular diseases that may represent low-grade ischemic insult [4,11,13]. However, scarce information exists on the utility and feasibility of DWI applications in patients with CAS.

Carotid stenosis is associated with hemodynamic cerebral ischemia. Therefore, we investigated the impact of unilateral internal CAS (ICAS) on brain parenchyma. The aim of this study was to investigate (a) whether WMLs and water diffusibility (ADC values) in NAWM differ between ipsilateral and contralateral hemispheres, (b) whether ADC values are related to WMLs and common vascular risk factors, and (c) whether ADC values differ between hemispheres after CEA without a shunt.

2. Material and methods

Patients with unilateral ICAS who were undergoing carotid endarterectomy were prospectively recruited. The study was approved by the Local Research Ethics Committee, and all patients (or their relatives) gave written informed consent.

2.1. Patients

Using carotid computed tomography angiography (CTA), carotid MR angiography (MRA), and/or carotid digital subtraction angiography (DSA), a total of 32 patients were identified as having unilateral ICAS. Two patients with confluent infarction were excluded because of inadequate analysis for ADC values, and two patients were excluded because of motion artifacts. In addition, three patients were excluded because of the absence of postoperative imaging. Finally, a total of 25 consecutive patients with unilateral ICAS were included in the present study. ICA stenosis was determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. All patients met the following inclusion criteria: (1) ≥70% stenosis in unilateral ICA, (2) less than 50% stenosis in contralateral ICA, and (3) no history of ICA stenosis treatment and absence of potential cardiogenic origin for emboli. Baseline demographics of the patients and medical data were prospectively acquired. Vascular risk factors, such as diabetes, coronary artery disease, hypercholesterolemia, lower extremity peripheral arterial disease, hypertension, and cerebrovascular disease (previous stroke or transient ischemic attack) were recorded. Smoking status was categorized as former, never, or current. Vascular risk factors were determined according to standard clinical guidelines as previously described [14].

2.2. MR imaging protocol

MR imaging was performed on a 1.5 T clinical scanner (Espree; Siemens, Erlangen, Germany) using a 12-channel phased array head coil the day before and within 2 days after CEA. The preoperative MRI protocol included the following axial sequences: (1) fluid-attenuated inversion recovery (FLAIR, TR/TE/TI = 11.000/140/2600, section thickness = 3.0 mm), (2) T1-weighted inversion recovery (TR/TE/TI 6000/25/300, section thickness = 3.0 mm), (3) variable-echo, fast spin echo (TR/TE1/TE2 = 5500/20/90, section thickness = 3.0 mm), (4) diffusion-weighted imaging (DWI) with a spin-echo echo-planar imaging sequence (TR/TE = 4200/114, section thickness = 5.0 mm, flip angle = 90°). Diffusion was measured in three orthogonal directions (x, y, and z) with b values of 0, 500, and 1000 s/mm^2. ADC maps were automatically generated using a pixel-by-pixel approach. For all sequences, the FOV was 230 mm × 230 mm and the matrix was 256 × 256. Variable-echo and T1-weighted images were obtained with the same orientation as the FLAIR images. The postoperative MRI protocol included DWI and FLAIR sequences with the same parameters.

Table 1
WML scoring system.

White matter (WM) lesions	
1.	Periventricular WM (frontal, parietal, and occipital) 0 = none, 1 = <5 mm thick, and 2 = >5 mm thick
2.	Deep WM (frontal, parietal, temporal, occipital)
3.	Basal ganglia (BG) (lentiform nucleus (LN), caudate nucleus (CN), thalamus, internal capsule)
4.	Brain stem (cerebellar WM, midbrain and pontine reticular formations, medulla) *For 2, 3, and 4* 0 = none; 1 = 5 or fewer ≤3 mm, 2 = 6 or more ≤ 3 mm, 3 = 5 or fewer 4–10 mm, 4 = 6 or more 4–10 mm, 5 = ≥11 mm, and 6 = confluent

2.3. Data analysis

All images were transferred to a separate imaging workstation (Leonardo; Siemens Medical Solutions). Two radiologists (N.S., A.S.) who were blinded to the clinical data with 10 and 18 years of experience in neuroradiology, respectively, reviewed all images independently and recorded old infarcts. All image analyses were then compared; disagreements were resolved through consensus.

White matter lesions were analyzed on all matched sequences and were rated using Scheltens scale as the scoring system [15]. This scale has four subscales, including evaluation of periventricular and deep white matter, basal ganglia, and brain stem. A modified version of the scale was used as previously described [7] in which WMLs of the lentiform nucleus were rated in a single group without further classification into the globus pallidus and putamen. The details are shown in Table 1. ADC measurements were performed based on consensus of the same two observers. Four regions of interest (ROI) were drawn in each hemisphere including anterior and posterior periventricular white matter, thalamus and occipital white matter (Fig. 1). ROIs were first drawn on the T2-weighted ($b = 0$) images and they were subsequently transferred onto the corresponding ADC maps. Care was taken to avoid contamination of the ROIs with any T2-weighted signal intensity changes. The area of each ROI was 0.3–1 cm^2.

2.4. Statistical analysis

Differences in WML scores and preoperative ADC values between the ipsilateral hemisphere with ICA stenosis and contralateral hemisphere without significant stenosis were assessed by the Wilcoxon signed-rank test. In addition, preoperative and postoperative ADC values were compared in each hemisphere by the Wilcoxon signed-rank test. Spearman's Rho correlation test was performed to determine associations between ADC values, WML scores and explanatory variables (e.g., age, sex, and vascular risk factors).

All probability values were two-tailed; $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 20.0 (Armonk, NY, USA: IBM Corp).

3. Results

Representative images of WML scoring and corresponding ADC measurements are shown in Figs. 2 and 3.

Twenty-five patients (16 men, 9 women) had unilateral ICA stenosis and had a mean age of 68.04 (±8.97) years. Table 2 demonstrates the baseline characteristics of the study sample.