# Volumetric Distribution of the White Matter Hyper-Intensities in Subject with Mild to Severe Carotid Artery Stenosis: Does the Side Play a Role?

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*Purpose:* The purpose of this paper was to assess the difference in the distribution of white matter hyperintensities (WMHs) on left and right sides of the brain hemispheres of subjects with mild to severe carotid artery stenosis. *Material and Methods:* Eighty consecutive patients (mean age 71 ± 6 years, males 66) with carotid artery stenosis were prospectively recruited. FLAIR-WMH lesion volume was performed using a semiautomated segmentation technique (Jim, Xinapse System, Leicester, UK). The Wilcoxon test was applied to verify the differences in the volume of WMHs between the right and left hemispheres. *Results:* A statistically significant difference was found in the middle cerebral artery (MCA) territory for the volume of the lesions (median volume of WMHs of the left side = 889.5 $mm^3$; median volume of WMHs on the right side = 580.5 $mm^3$; $P = .0416$); no statistically significant difference was found on the other territories by taking into considerations the lesions. By analyzing the degree of stenosis, we found a higher degree of stenosis of the left side (67.9%; 95% confidence interval [CI], 64.8%-70.9%) compared with the right side (65.7%; 95% CI, 62.4%-68.9%), but the Mann–Whitney test did not show a statistically significant difference ($P = .3235$). *Conclusions:* Results of our study suggest that there is a difference in the distribution of WMHs in the brain hemispheres according to the left/right side on the MCA territories and for the periventricular white matter in subjects with mild to severe carotid artery stenosis.
**Key Words:** Carotid artery—white matter—leukoaraiosis—magnetic resonance.


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Received January 11, 2018; revision received February 16, 2018; accepted February 28, 2018.

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1052-3057/$ - see front matter



https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.02.065

## Introduction

The term "white matter hyperintensities" (WMHs) indicates the presence of hyperintensities on T2-weighted images in the white matter.[1] WMH is commonly encountered in the brain of elderly patients[1] and in the general population. Its prevalence ranges from 11% to 21% in adults aged around 64 years to 94% at the age of 82 years.[2,3]

Previously pathology-published studies found that those areas where WMH is detected are characterized by the presence of tissue rarefaction associated with loss of myelin and axons; in some cases, findings show a moderate degree of gliosis.[4,5]

A higher prevalence of WMH was found in subjects with hypertension and cerebrovascular risk factors,[6-8] and this parameter is commonly used to assess cerebrovascular burden in cognitive impairment[9] and appears to be associated with an increased risk of cognitive decline.[10]

In the past years the WMH presence and degree of severity were assessed with qualitative scales[11] based on the subjective assessment of the observer, whereas nowadays, thanks to the development of automated and semiautomated software, it is possible to quantify the volume of WMHs[12,13] in cubic millimeters.

In the last years, studies have demonstrated that a statistically significant higher prevalence of cerebrovascular ischemic events involves the left hemisphere more than the right[14-16] by showing that the left side plays a significant role in the risk of developing ischemic events. Recently, a study showed that carotid atherosclerotic plaque size and composition (in particular the intraplaque hemorrhage) are not symmetrically distributed, with the left-sided plaques being more vulnerable.[17]

We aimed to assess the volumetric distribution of the WMHs in the left and right hemispheres according to the different arterial territories (anterior cerebral artery [ACA], middle cerebral artery [MCA], and posterior cerebral artery [PCA]) and to the involvement of periventricular white matter (PVWM) or deep white matter (DWM).

## Material and Methods

### *Study Design and Patient Population*

The Institutional Review Board approval for this study was obtained, and patients' consent was waived because of the retrospective nature of the study. Based on a power calculation (type I error, $\alpha = .05$; type II error $\beta = .1$; Az Null Hypothesis value = .5; Az significant value = .7, pooled group), we estimated that a sample size of at least 145 hemispheres would be sufficient to investigate the potential difference in the volumetric distribution of the WHMs in the left and right hemispheres according to the different arterial territories. We decided to also include a correction of 10%, and therefore, we included 80 consecutive patients (for 160 brain hemispheres) who underwent brain magnetic resonance imaging (MRI) in our hospital form March 2012 to December 2013 (66 men, 14 women; mean age, 71 years; age range 48-83 years).

Patient selection restricted to persons with carotid atherosclerosis and the subjects were selected by our database by considering those subjects aged more than 40 years who had a brain MRI because of the presence of atherosclerotic disease in the carotid arteries documented by using ultrasonography. In our institute those patients who showed an atherosclerotic disease that determines a stenosis degree > 30% according to the North American Symptomatic Carotid Endarterectomy Trial criteria[18] were invited to undergo an MRI exam of the brain.

To quantify the stenosis degree using CTA, oblique axial images normal to ICA lumen centerline were elaborated and the value was calculated by comparing the diameter of the stenosed segment with the most distal normal one, where no stenosis was present.

We considered the following as exclusion criteria: (1) other possible etiologies for white matter disease, such as vasculitis, demyelinating diseases, and connective tissue diseases; (2) concomitant pathologies such as brain tumor, abscess, and encephalitis; (3) strokes (as reported by clinical charts with brain MRI/computed tomography confirmation of stroke); (4) the presence of cardioembolism documented by cardiologists; and (5) absolute MRI contraindications.

Part of the examined population was included in previously published studies.

### *Brain MRI Technique*

Brain MRI examinations were performed according to a previously described technique[19] on a Gyroscan 1.5-T MRI scanner (Philips, Best, The Netherlands) with a head coil. As part of our general brain protocol, axial and sagittal 2D FLAIR images (10,000/140/2200 msec for TR/TE/TI; matrix: 512 × 512; FOV: 240 × 240 $mm^2$; section thickness: 5 mm) were obtained and used for the determination of WMH volume. Also T1-weigheted and T2-weigheted images were considered in order to exclude chronic silent brain infarcts.

### *MRI WMH Volume and Number Analysis*

The volumetric measurement of the WMHs was performed using a semiautomated segmentation technique (Jim, Xinapse System, Leicester, United Kingdom). The axial FLAIR images were selected, and 1 experienced neuroradiologist performed the analysis by considering hyperintense white matter regions on FLAIR images not related to large vessel infarcts as WMHs. The neuroradiologist was blinded for the main purpose of this study and to the clinical data. After the delineation of WMHs, the WMH volumes for each hemisphere were automatically produced by the software, based on the slice thickness and outlined WMH areas. The number of lesions for each hemisphere was calculated. Moreover, the same neuroradiologist classified the WMHs according to the different arterial territories (ACA, MCA, and PCA) and to the involvement of the PVWM or the DWM.

The regions assessed for WMHs were the frontal, parietal, occipital, and temporal lobes, basal ganglia, and infratentorial regions. DWM included frontal, parietal, occipital, and temporal regions, whereas PVWM included lesions in 3 regions (frontal and occipital caps and bands), and a periventricular lesion was operationally defined as adjacent to the ventricle.

Lacunar silent brain infarcts were excluded from the analysis and were identified according to Vermeer et al's[20] classification, in whom lacunar infarctions were defined as well-defined small focal lesions, most commonly located