Journal of the Neurological Sciences 334 (2013) 77–82

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

# The effect of white matter lesions on cognition after carotid revascularization

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ARTICLE INFO

*Article history:*
Received 4 May 2013
Received in revised form 21 June 2013
Accepted 25 July 2013
Available online 11 August 2013

*Keywords:*
Angioplasty and stenting
Carotid endarterectomy
Carotid artery disease
Cognition
White matter disease
Follow-up

ABSTRACT

*Background:* Cerebral white matter lesions (WML) are associated with cognitive impairment, and carotid revascularization with cognitive worsening or improvement. We assessed the relation between WML severity and changes in cognition after carotid endarterectomy or stenting.

*Methods:* Patients with symptomatic carotid artery stenosis, enrolled in the International Carotid Stenting Study (ISRCTN25337470), underwent detailed neuropsychological examinations (NPEs) before and after 6 months. Cognitive results were standardized into z-scores, from which a sum score was calculated. The primary outcome was the mean difference (MD) in sum score between baseline and follow-up. Changes in sum score were related to WML severity with the 'age-related white matter changes' score, assessed on baseline MRI-FLAIR. Three groups were formed based on this score.

*Results:* Eighty-nine patients had both baseline MRI and NPE, of these 77 had a calculable cognitive difference score. The cognitive sum score at six months was worse than at baseline: MD, −0.21; 95% CI, −0.32 to −0.09. The change in sum score did not depend on WML load: MD for no-to-mild WML, −0.15; 95% CI, −0.39 to 0.09, for moderate WML, −0.27; 95% CI, −0.48 to −0.06; and for severe WML, −0.21; 95% CI, −0.40 to −0.04. This did not change essentially after adjustment for baseline factors.

*Conclusion:* Cognitive functioning deteriorated after carotid revascularization, regardless of baseline WML burden.


## 1. Introduction

Cerebral white matter lesions (WML) have been associated with cognitive deficits [1–4], particularly with disturbances in executive functioning, attention, naming, and visuoconstructional praxis [2,5], but also in mental speed and on global measures of cognition [2,4,5]. The prevalence and severity of WML increase with age [6–8] and with the presence of hypertension [6,9] or diabetes [10]. WML are correlates of small vessel disease on imaging of brain parenchyma, encompassing ischemic and hemorrhagic lesions [11]. One probable pathophysiological mechanism is that a decrease in vessel lumen leads to chronic hypoperfusion of the white matter, eventually resulting in cell degeneration and cell death [11].

In some studies, the severity of WML has been associated with the extent of atherosclerosis in the carotid artery [3,12,13], but others did not find this association [8]. Internal carotid artery stenosis has also been associated with cognitive impairment [3], and some authors have reported improvement in cognition after carotid revascularization [14]. However, such improvement was not observed in all studies [14], and in a recent substudy of the randomized International Carotid Stenting Study (ICSS) [15], carotid artery stenting (CAS) had a small detrimental effect on cognitive functioning at six months after treatment, whereas carotid endarterectomy (CEA) had no effect on cognition [16].

Because of the reported interrelation between carotid artery stenosis, WML, and cognitive impairment, we tested the hypothesis that the severity of WML at the time of carotid revascularization might influence cognitive performance at six months, with an improvement in patients with no or minor WML at baseline and no improvement or worsening in

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http://dx.doi.org/10.1016/j.jns.2013.07.2512

patients with a higher WML load, due to a reduced "cognitive reserve" in these patients.

## 2. Methods

The study population consisted of participants who were recruited simultaneously in the cognition substudy [16] and in the MRI substudy [17] of ICSS (ISRCTN25337470) [15,18] between February 2006 and December 2008 at the University Medical Center Utrecht (UMCU) and the Academic Medical Center in Amsterdam (AMC), the Netherlands. Patients were considered eligible for neuropsychological examination (NPE) if there was neither a language barrier nor pre-existent cognitive decline. Patients were excluded if they did not have any revascularization procedure after randomization. The institutional review boards of these centers had approved both studies, and written informed consent was obtained from each patient.

### *2.1. Patients and procedures*

Patient criteria and procedures in ICSS have been reported earlier [15,18]. In short, patients with recently symptomatic ICA stenosis of at least 50% [19] were randomly assigned to CAS or CEA. Data on presenting symptoms, demographic characteristics, and cardiovascular risk factors were collected. The National Institutes of Health Stroke Scale (NIHSS) [20] was assessed at baseline and at one day after treatment, and the modified Rankin Scale (mRS) [21] at baseline and at one and six months after treatment.

### *2.2. Neuropsychological assessment*

The neuropsychological tests used to assess cognition in this study have been reported previously [16]. Cognition was assessed in the week preceding treatment and after six months by means of an extensive NPE that consisted of 15 tests, resulting in 20 test measures representative for the major cognitive domains according to Lezak, i.e. abstract reasoning, attention, executive functioning, language, verbal memory, visual memory, visual perception, and neglect [22]. By combining performance over tasks and cognitive domains, we also assessed cognitive integrity or 'mental effort' by means of tasks that go beyond the scope of the corresponding cognitive domain itself [23]. That is, evaluation of functions where many different cognitive abilities are needed for optimal performance including mental speed, attention, executive functioning, planning, and overview capacity and cognitive flexibility. This construct of 'mental effort' consisted of the following tasks: Boston Naming Task, Verbal Fluency (Letters 'N' and 'A' in 1 min), the Visual Elevator Subtest of the Test of Everyday Attention, the Rey-Osterrieth Complex Figure (copy and delayed recall trial) and the Benton Judgment of Line Orientation test.

Measures of mood states for depression were tested with the Beck's Depression Inventory (2nd Ed.) [24], and of anxiety with the State and Trait Anxiety Inventory [25]. Higher assessment scores indicate a higher measure of anxiety or depression. Pre-existent cognitive decline was assessed by means of the Informant Questionnaire of Cognitive Decline [26]; where everyday situations are rated by a relative for amount of cognitive change over the past 10 years and a score above 3.6 is likely to be related to dementia. Furthermore, estimates for current general cognitive functioning (Mini Mental State Examination) were obtained [27].

### *2.3. Test result transformation*

Individual test scores were transformed into standard deviation (SD) units – z-scores – based on the mean and SD of a control group [28]. The control group consisted of healthy individuals who had performed the same NPE and were retested after an identical time interval, hereby controlling for potential practice effects in our patients. Control subjects were free from pre-existent neurological, psychiatric or cognitive abnormalities. The z-score for each domain was derived by calculating the mean of the z-scores comprising that domain. Also, as a measure of overall cognition, a cognitive sum score was calculated, representing the mean over the eight major cognitive domains [22]. Negative domain scores at baseline express a score below the mean of the control group. To assess the cognitive change over time, difference scores were calculated by subtracting the baseline values from the scores at follow-up. Therefore, negative domain or sum change scores indicate a decrease from baseline.

### *2.4. Imaging*

Magnetic resonance imaging (MRI) was performed one to three days before treatment. MRI parameters, WML data, and lesion measurements have been reported earlier [17]. Baseline WML were semiquantitatively assessed on fluid-attenuated inversion recovery (FLAIR) sequences using the Age-Related White Matter Change (ARWMC) score, which has a good intra- and interrater reliability [29,30]. An ARWMC sum score was calculated afterwards (range 0–30). Based on the sum ARWMC score, patients were divided into groups according to tertiles in the current patient group: no-to-mild ARWMC $\leq 3$ (WML−), moderate ARWMC = 4–5 (WML+), and severe ARWMC $\geq 6$ (WML++).

### *2.5. Outcome measures*

The primary outcome measure of this study was the change in cognitive sum z-score between baseline and follow-up, expressed as a mean difference (MD). Secondary outcome measures were the change(s) per cognitive domain z-scores.

### *2.6. Statistical analysis*

Descriptive statistics were performed on patient characteristics at baseline in the three WML categories. We compared cognitive change between baseline and follow-up between the three WML groups with linear regression in which we used two dummy variables for the non-normally distributed WML classes. Differences between the WML groups were calculated with accompanying 95% confidence intervals (CIs) and were adjusted for age, sex, and education. In a separate model we additionally adjusted for baseline imbalances between the groups (history of coronary artery bypass grafting, presenting TIA's or symptoms involving an eye). Negative difference scores between the groups indicate a worse performance in comparison with the reference group, i.e. the "no-to-mild WML" category. We calculated the unadjusted change within the different WML groups with the paired *t*-test.

## 3. Results

### *3.1. Patient flow*

Fig. 1 shows the patient flow, and provides reasons for exclusion. A total of 151 patients were eligible to participate during the study period. Eventually, 78 patients had both MRI imaging and a follow-up NPE. The study population consisted of the 77 patients with a calculable cognitive difference score, because in one subject the baseline examination was found unreliable due to symptoms of the presenting stroke. Patients without follow-up NPE were 8.2 years older compared with those who were tested at follow-up (95% CI, 3.1 to 13.2), but they did not differ with regard to the ARWMC sum score (mean difference (MD) 2.1, 95% CI −1.1 to 5.4) and other demographic, clinical, and cognitive characteristics (data not shown). The two raters agreed on the ARWMC score in 197 of 231 (85.3%) cases.