Journal of the Neurological Sciences 328 (2013) 58–63

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

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

Diffusion-weighted lesions after carotid artery stenting are associated with cognitive impairment

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A R T I C L E I N F O

Article history:
Received 5 October 2012
Received in revised form 24 January 2013
Accepted 21 February 2013
Available online 17 March 2013

Keywords:
Carotid artery stenting
Cognitive performance
DWI lesion

A B S T R A C T

The effect of carotid artery stenting (CAS) on cognitive function is still debated. Cerebral microembolism, detectable by post-procedural diffusion-weighted imaging (DWI) lesions, has been suggested to predispose to cognitive decline. Our study aimed at evaluating the effect of CAS on cognitive profile focusing on the potential role of cerebral microembolic lesions, taking into consideration the impact of factors potentially influencing cognitive status (demographic features, vascular risk profile, neuropsychological evaluation at baseline and magnetic resonance (MR) markers of brain structural damage). Thirty-seven patients with severe carotid artery stenosis were enrolled. Neurological assessment, neuropsychological evaluation and brain MR were performed the day before CAS (E0). Brain MR with DWI was repeated the day after CAS (E1), while neuropsychological evaluation was done after a 14-month median period (E2). Volumes of both white matter hyperintensities and whole brain were estimated at E0 on axial MR FLAIR and T1w-SE sequences, respectively. Unadjusted ANOVA analysis showed a significant CAS∗DWI interaction for MMSE ($F = 7.154(32)$, $p = .012$). After adjusting for factors potentially influencing cognitive status CAS∗DWI interaction was confirmed for MMSE ($F = 7.092(13)$, $p = .020$). Patients with DWI lesions showed a mean E2–E0 MMSE reduction of −3.1, while group without DWI lesions showed a mean E2–E0 MMSE of +1.1. Our study showed that peri-procedural brain microembolic load impacts negatively on cognitive functions, independently from the influence of patients-related variables.

1. Introduction

The effect of carotid artery stenting (CAS) on cognitive function is still debated. Independent studies reported different findings: improvement [1], deterioration [2], or stability of cognitive performance following CAS [3]. Although cerebral microembolism, detectable by early post-procedural diffusion-weighted imaging (DWI) lesions, has been suggested to predispose to cognitive decline [4], the reported results are conflicting [5], probably due to methodological and patient-related variables discrepancy [6].

Magnetic resonance (MR) studies described higher incidence of clinically silent DWI lesions in patients with vascular dementia and recent cognitive deterioration [7]. Furthermore, silent microembolic cerebral injury seems to be associated to cognitive impairment occurring after cardiac catheterization and surgical procedures [8].

In patients undergoing CAS also vascular risk factors for dementia, such as hypertension, diabetes, hypercholesterolemia and smoking, might influence cognitive profile [9] or act synergically with carotid disease to induce cognitive impairment [10].

Carotid disease is associated with MR indices of brain vascular damage, such as white matter hyperintensities (WMH) detected by fluid attenuated inversion recovery (FLAIR) [11]. Moreover, WMH volume is related with an increased risk of dementia [12] and global brain atrophy although it is not yet clear whether this association is independent of shared risk factors [13].

Our study aimed at evaluating the effect of CAS on cognitive profile and the potential role of cerebral microembolism, embodied by post-procedural DWI lesions. The impact of patient-related factors potentially influencing cognitive status (demographic features, vascular risk

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http://dx.doi.org/10.1016/j.jns.2013.02.019

profile, neuropsychological evaluation at baseline and MR markers of brain structural damage) was also investigated.

2. Methods

Thirty-seven patients (mean age 72.9 ± 7.9 years, 13 female) with severe (i.e. greater than 70%) carotid artery stenosis, diagnosed in our ultrasound laboratory according to standardized criteria [14] and selected for carotid angioplasty with stent placement, underwent this procedure at the Interventional Radiology of our institution from January 2007 to November 2011.

Plaque characteristics and degree of stenosis were always confirmed by computed-tomographic angiography of the neck vessels. Intracranial vessels were also examined with transcranial color-coded sonography and MR angiography: no patient had significant stenosis of the large intracranial arteries.

All patients underwent electrocardiogram and cardiological examination at admission. Neurological assessment including National Institutes of Health Stroke Scale (NIHSS), neuropsychological evaluation and brain MR were performed the day before CAS (E0). No patient had recent (<3 months) stroke or transient ischemic attack or possible or probable embolizing cardiopathy. Three patients had a mild stroke 6 months before the procedure: two patients had a NIHSS score = 1 point, the third one had a NIHSS score = 3 points at E0.

CAS procedures were performed according to the European guidelines [15].

The day after the procedure (E1), clinical assessment and brain MR were repeated and color-coded duplex sonography of the neck vessels was performed to evaluate CAS good outcome. In addition, all patients underwent continuous electrocardiographic monitoring in the first 48 h following CAS to detect possible arrhythmias (in particular, new onset of atrial fibrillation or bradycardia <40 bpm).

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. Patients were followed-up by telephone interview every 3 months and clinically re-evaluated after 6 months.

The study was approved by the institutional review committee and was performed according to the ethical standards laid down in the 1964 Declaration of Helsinki. All the patients gave their informed written consent.

2.1. MR imaging

MR was performed with an Achieva 1.5 T scanner (Philips Medical Systems, Best, the Netherlands) and an 8 channel head phase-array coil with parallel imaging capabilities (SENSE). The following brain MR sequences were collected both at E0 and E1: axial plane T1w-SE (T1w-spin echo; TR = 550, TE = 15, slice thickness = 3 mm, interslice gap = 0), FLAIR (TR = 8000, TE = 125, TI = 2500; slice thickness = 3 mm, interslice gap = 0), and DWI (TR = 3220, TE = 88, b value = 1000, slice thickness = 5 mm, interslice gap = 1 mm) with apparent diffusion coefficient (ADC).

Total WMH volume was computed on FLAIR axial images at E0, after having segmented lesional region of interests (ROIs) through a semi-automated local thresholding approach (Osirix® software V.3.9.4) (Fig. 1) [16].

Whole brain volume (WBV) normalized for subject head size was estimated with SIENAX [17] version 2.6 (part of FSL 4.1.9, FMRIB's software library) on the axial T1w-SE sequences acquired at E0.

After the procedure (E1) DWI was looked over for areas of restricted diffusion (DWI lesions) (Fig. 2). If present, total number and anatomical localization of DWI lesions were considered. They were further classified according to the side of the treated artery (ipsilateral or contralateral), vascular territory (anterior cerebral artery—ACA, posterior cerebral artery—PCA, and middle cerebral artery—MCA, or border zones) and cortical or subcortical location. Border zones were considered as external (cortical), if located at the junctions of ACA, PCA and MCA territories, or internal (subcortical), at the junctions of the three cerebral artery territories with the Heubner, lenticulostriate, and anterior choroidal artery [18].

MR imaging analysis was conducted by the consensus of two investigators blind to clinical patients' data.

2.2. Neuropsychological evaluation

Memory, attention, executive functions and language were evaluated at E0 and after a median of 14 months (min 4–max 41) from CAS (E2). Cognitive global function was assessed by Mini-Mental State Examination (MMSE). Episodic verbal memory was studied with Rey's Auditorial Verbal Learning Test (RAVLT). The numbers of words recalled after the first presentation of a 15-word list was used as a marker of short term verbal memory (RAVLT—Immediate, RAVLT-I), while the number of words recalled after an interference visuo-spatial task was considered a marker of long-term verbal memory (RAVLT—Delayed, RAVLT-D). Recall of Rey–Osterrieth Complex Figure Test (RROF) was used as an index of long-term episodic visual memory. Attention was examined by Double Barrage Test (DBT), expressed in seconds needed to perform the task. The linguistic skills were evaluated with battery for the analysis of the aphasic deficit subtest (oral denomination names—ND), while executive functions were examined by Raven's progressive matrices test (RPM).

For each administered test appropriate adjustments for age and education were applied according to normative data of the Italian population [19]. Available cut-off scores of normality (95% of the lower tolerance limit of the normal population distribution) were applied. The difference between post-procedural and pre-procedural values was computed (E2–E0).

2.3. Statistical analysis

The differences between post-procedural and pre-procedural values (E2–E0) of each cognitive domain were compared between DWI and non-DWI group by means of independent Student's *t*-test.

For differences in MMSE, non-parametric descriptive (median, min–max) and inferential (Mann–Whitney test) statistics were applied.

To assess the effects of CAS (two levels: E2, and E0), DWI (occurrence of new DWI lesions) and their interaction on cognitive measures, ANOVA for repeated measures was applied with CAS as within-subjects factor and DWI as between-subjects factor. To take into account the influence of demographic variables (age, and years of education), vascular risk factors (smoking, hypertension, diabetes, and hypercholesterolemia), follow-up length, and basal MR findings (WMH volume and WBV) on cognitive profile, these variables were entered as covariates in the adjusted ANOVA model. Moreover, E0 cognitive domain scores were added as covariates in adjusted ANOVA analysis for each corresponding cognitive test. To provide information about the changes that occurred, 95% confidence intervals were also computed. Chi-square and independent samples *t*-test were used to compare groups based on DWI lesions.

A formal power analysis was not performed in advance. If DWI lesion occurrence reached 50%, a sample size of 30 patients provides a power of 0.80 to recognize as statistically significant (at bilateral alpha level 0.05) only large effect sizes. The power decreases if DWI lesion occurrence is less. Thus, this study should be considered as explorative, being not able to detect smaller yet clinically relevant differences. Statistical analysis was performed with SPSS software (version 19) for Windows.

3. Results

Table 1 shows patients' demographic and lifestyle characteristics, atherosclerosis burden, MR findings and cognitive status at baseline.