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The effect of severe carotid occlusive disease and its surgical treatment on cognitive functions of the brain

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ABSTRACT

Surgery of a high-grade carotid stenosis is evidence-based stroke prevention. Also cognitive effects are reported after carotid endarterectomy (CEA): both deterioration and improvement, the former attributed to perioperative complications and the latter often to learning effect. By imaging, brain perfusion and diffusion changes were shown in subjects with a high-grade stenosis undergoing CEA. We wanted to find out if the cognition of patients undergoing CEA display postoperative worsening or true improvement in association with findings in serial MR imaging. The patients had a poorer overall cognition than healthy matched controls. The cerebral hemisphere ipsilateral to the stenosis had higher diffusion and more sluggish perfusion leading to perfusion deficits. These asymmetries were abolished by CEA. Postoperatively, the patients showed a trend for cognitive worsening, most often attentional, but over months, the group performance improved similarly to the controls. Still, lower baseline perfusion was associated with a greater cognitive improvement, most clearly in executive functions. Consequently, despite the risk for transient decline, true cognitive benefit by CEA seems possible.

1. Introduction

Carotid endarterectomy (CEA) is evidence-based prevention of ischemic stroke and has been suggested to affect cognition (Chaturvedi et al., 2005). Earlier studies tended to report cognitive improvement, but it may have been due to learning effect in repeated testing; furthermore, many studies have reported no change or worsening, and so the possibility of true improvement is still unresolved (Bossema, Brand, Moll, Ackerstaff, & van Doornen, 2005; Lunn, Crawley, Harrison, Brown, & Newman, 1999). Even in a study reporting postoperative cognitive improvement, it could not be attributed to increased cerebral blood flow (Hemmingsen et al., 1986). To the contrary, the recent reports have predominantly suggested at least a transient cognitive decline in a substantial proportion (Heyer et al., 2002; Heyer et al., 2006; Mocco et al., 2006). CEA is a risk factor for stroke itself although the risk is small in skilled hands, and the reported cognitive decline is often attributed to subtle perioperative embolization or hemodynamic instability (Crawley et al., 2000; Gaunt et al., 1994). The postoperative decline is mostly MRI-negative, although relatively silent embolization seems to occur in at least one-tenth of patients in diffusion-weighted imaging (DWI) (Heyer et al., 2002; Heyer et al., 2006; Wolf et al., 2004).

We have previously shown that carotid stenosis (CS) is associated with changes in DWI and perfusion-weighted imaging (PWI): in PWI, the mean transit times (MTT) were longer especially in patients with symptomatic stenoses producing visible deficits in perfusion maps in the most affected subjects, and the findings were improved by CEA (Soinne et al., 2003). In DWI, the average apparent diffusion coefficients (ADC_{av}) were higher in the ipsilateral hemisphere than in healthy subjects, also partly reversibly (Soinne et al., 2003). To elucidate the issue of cognitive change, we studied the association of DWI and PWI findings and white matter hyperintensities (WMHI) on conventional MR images with cognitive performance of patients undergoing CEA for a high-grade CS to find out if (1) the patients' cognitive functioning before and after CEA is different from healthy controls, taking into account the learning effect in repeated testing, (2) if the cognitive change is related to altered perfusion or diffusion in the brain, and (3) if the cognitive change after CEA is predicted by the preoperative imaging.

2. Subjects and methods

2.1. Characteristics

This study was carried out as a substudy of the Helsinki Carotid Endarterectomy Study (HeCES) recruiting consecutive patients re-

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ferred to the Departments of Neurology and Cardiovascular and Thoracic Surgery, fulfilling the study criteria: independence in daily life, no potential cardiogenic origin of emboli, no history of previous ipsilateral CEA or radiotherapy, and with a surgically accessible unilateral CS measuring 70% or more in digital subtraction angiography (NASCET criteria). The study was approved by the local Ethics Committee, and it followed the principles of the Declaration of Helsinki and the institutional guidelines. All subjects gave written informed consent, and they underwent CEA within the study. In this substudy, we recruited 44 patients with either symptomatic ($n = 21$) or asymptomatic ($n = 23$) high-grade CS to undergo repeated imaging and neuropsychological evaluation. The subjects underwent a thorough clinical assessment by a stroke neurologist before CEA, and 4 and approximately 100 days after CEA. In the asymptomatic stenosis group (ACS), no patient had a history of transient ischemic attack (TIA) or stroke. In the symptomatic stenosis group (SCS) the qualifying event was TIA in 14 patients and minor stroke in 7 patients. The demography and risk factor profiles are given in Table 1. None had significant angiographic stenoses in intracranial vasculature.

2.2. Control population

The patients were sorted by criteria of age, sex, education, and social class, and a control person was selected for every second patient. The 22 control subjects consisted of strictly healthy volunteers, recruited by word of mouth, fulfilling the following criteria: no symptom, sign or history of any neurological disease or a systemic disease with a potential brain involvement; no family history of dementia or multiple sclerosis; no regular medication, and no history of excessive alcohol intake over longer periods. They were matched for age (±5 years), sex, and education and/or social class classified with three-category scales (Table 1) (Rahkonen, Arber, & Lahelma, 1995). Half of the control population had taken part in a previous MRI study of healthy humans with normal scanning results and no sign of CS (Helenius et al., 2002).

2.3. Anesthesia and surgery

All patients were operated under general anesthesia with routine hemodynamic and transcranial Doppler monitoring by the same surgeon with a standard approach. Sedation, induction, muscle relaxation, and maintenance of anesthesia were carried out according to the hospital practice. Shunting was performed in three patients on the basis of stump pressure.

Table 1
Clinical profiles of the patients and controls at baseline (±*SD*)

	Patients	Controls
Age	65.3 (±8.4)	67.0 (±8.9)
Body mass index	26.4 (±4.2)	25.5 (±4.2)
Cerebrovascular events		
Stroke	7 (16%)	0
TIA	14 (33%)	0
None	23 (51%)	22 (100%)
Gender (female/male)	16/28	9/13
Education (years)	9.6 (±3.2)	10.2 (±4.8)
Higher	5 (11%)	4 (18%)
Secondary	16 (36%)	8 (36%)
Basic	23 (52%)	10 (45%)
Social class		
Non-manual	12 (27%)	6 (27%)
Skilled manual	20 (46%)	11 (50%)
Unskilled manual	12 (27%)	5 (23%)
Arterial hypertension	16 (70%)	0
Coronary heart disease	9 (39%)	0
Diabetes	8 (35%)	0
Peripheral arterial disease	7 (30%)	0

2.4. Neuropsychological assessment

The cognitive assessment was done on the day before CEA, 4 days after the operation (5.0 days after baseline), and at approximately 100 days (mean 102), in the same quiet room at approximately the same daytime, by either of two certified neuropsychologists. The control population was examined thrice with the same timing. The same examiner was used for repeated evaluations, and all controls were examined by the same examiner at all stages. The comprehensive neuropsychological battery was completed in the same order, using parallel forms of tests in a randomly crossed fashion when applicable.

The test battery was designed using validated tests (Lezak, 1995). Language domain was assessed by The Boston Naming Test (BNT) as naming and recognition of common objects (60), and word fluency with the letter and category naming with 1-min generation of words by a letter (WF-L) or by a category (WF-C). Verbal memory and learning were evaluated by Auditory Verbal Learning Test with 5 trials to learn 10-word lists, scoring both sum score of trials (AVLT-SUM) and delayed memory recall (AVLT-D) and immediate verbal memory with WAIS-R digit span forwards and backwards (W-VESP). Visual memory and learning by Rey Visual Learning Test scoring the sum of five trials as well as delayed recall (RVLT-SUM, RVLT-D), and immediate visual memory was evaluated with Corsi blocks visual span forwards and backwards (CB-VISP). Motor dexterity was evaluated with Purdue pegboard, scoring performance of the hand contralateral to the stenosis (PP-CONTRA). Attention was assessed with Letter Cancellation Task (LCT) and Trail Making A (TMA). Executive functions were assessed with the Trail Making and Stroop tests, making use of the differences of performance times in Trail Making A and B (TMB–TMA) as well as the word and colour naming in Stroop test (STROOP-INT) divided by the time spent on the first task. Mood was evaluated with Beck Depression Inventory.

Logarithmic transformation was applied to BNT and TMB–TMA, and square root transformation to STROOP-INT. The individual raw scores were standardized into *Z* scores using the controls' baseline performance as the norm, and inverted for the time-based tasks. Domain scores were derived as average *Z* scores of the subtests. The compound cognitive score (CCS) was calculated by summing up the individual *Z* scores and dividing by the standard deviation (*SD*) of summed scores (Table 2). Cognitive change scores were calculated by subtracting the baseline *Z* scores from the timely score, and then by subtracting the average learning effect of controls from this result and by dividing the result by the *SD* of the control group (Lewis, Maruff, & Silbert, 2004; Rasmussen et al., 2001). A worsening of more than one standard deviation of CCS was considered dysfunctional.

2.5. Imaging techniques and visual analysis

MR images were acquired on a 1.5 Tesla Siemens Magnetom Vision scanner. Axial DWI, dynamic susceptibility-contrast bolus tracking PWI, and conventional images were obtained. The first imaging was performed in the evening on the preoperative day, and it was repeated in close temporal proximity to cognitive assessments. DWI was performed with a spin-echo echo-planar imaging sequence having a repetition time of 4000 ms, an echo time of 103 ms, and a gradient strength of 25 mT/m covering 19 five-mm-thick slices (interslice gap 1.5 mm, field of view 230×230 mm^2, and matrix size $96 * 128$ interpolated to $256 * 256$). Diffusion was measured in three orthogonal directions