

Cognitive decline and cerebral vasoreactivity in asymptomatic patients with severe internal carotid artery stenosis

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Abstract The aim of the study was to correlate cognitive decline and cerebral vasoreactivity in 150 asymptomatic right-handed patients with severe $\geq 70\%$ unilateral internal carotid artery (ICA) stenosis and to evaluate the role of intracranial collateral circulation during cognitive testing. Cognitive assessment was performed by means of Montreal Cognitive Assessment (MoCA) and Mini Mental State Exam (MMSE) scales. Cerebrovascular reactivity (CVR) and intracranial collateral circulation were evaluated by means of breath holding index (BHI) and transcranial color Doppler (TCD) sonography. The results were compared with 150 right-handed controls matched for demographic variables and vascular risk factors. Patients with severe unilateral ICA stenosis had MMSE scores within a normal range, but MoCA scores were lower than normal. By examining the side of the observed stenosis, it has been noted that patients with left-sided ICA stenosis had lower MoCA scores in categories of language and episodic memory performance, while patients with right-sided ICA stenosis had lower MoCA scores in a category of visual-spatial skills. All patients had BHI values lower than normal. Subjects with a single intracranial collateral artery recruited had slightly better cognitive results than the

patients with two or more collateral arteries activated. Results of the study showed that altered cerebrovascular reactivity and cerebral hypoperfusion might be responsible for the reduction of specific cognitive functions ipsilateral to the ICA stenosis, therefore BHI and MoCA might be useful tools when screening for cognitive decline in asymptomatic patients with severe ICA stenosis.

Keywords Cognitive decline · Cerebral vasoreactivity · Severe internal carotid artery stenosis

Introduction

Cognitive decline in asymptomatic patients with severe ICA stenosis often remains unrecognized. In large population studies ICA disease has already been documented as an independent risk factor for mild cognitive impairment and it was not due to underlying vascular risk factors. In Cardiovascular Health Study cognitive impairment and decline were associated with asymptomatic high-grade stenosis of the left ICA, but high-grade stenosis of the right ICA was not associated with cognitive impairment [1]. In Tromso study most patients had right-sided stenosis or bilateral occlusion of carotid arteries. Subjects with carotid stenosis or occlusion had lower performance in several subsets of cognitive tests and some of the neuropsychological tests revealed graded relationship to a degree of the stenosis [2]. Progressive atherosclerosis commonly leads to multiple small strokes and subsequent brain damage causing vascular dementia [3, 4]. Risk factors for vascular dementia include non-modifiable risk factors: age, gender, previous myocardial infarction, TIA or stroke and modifiable risk factors—diabetes, hyperlipidemia, arterial hypertension, atrial fibrillation, coronary, cerebrovascular

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and/or peripheral artery disease, obesity, physical inactivity, stress, alcohol consumption and smoking. Because some of the risk factors are modifiable, it is of great interest to establish their influence on the severity of cognitive deficit and its possible prevention [5, 6]. There are two possible underlying pathomorphological mechanisms of cognitive changes in patients with carotid artery disease: cerebral emboli and hypoperfusion with or without silent brain infarctions, in both cases, the loss of regional cerebral autoregulation is manifested [7–9]. In patients with severe carotid artery disease, impaired cerebral autoregulation might be detected by means of TCD, using BHI for assessment of cerebral hemodynamics [10–12]. Furthermore, altered cerebrovascular reactivity and consecutive cerebral hypoperfusion may be responsible for reduction in cognitive abilities involving the function of the hemisphere ipsilateral to the internal carotid stenosis. Correlation between impaired cerebral small vessels functionality and decreased cognitive function has been demonstrated in patients with Alzheimer's disease. Also, decreased cerebrovascular reactivity correlated with advanced age and cognitive decline when evaluated by neuropsychological testing [13, 14]. Standard neuropsychological testing is created to test separate tasks to assess the various cognitive functions which are controlled by different brain regions. There is a correlation between advanced ICA stenosis and decreased score of neuropsychological tests, especially in executive functions. Cognitive evaluation is mostly performed by means of MMSE, a quick, but quite unfortunate method for MCI screening. On the other hand, MoCA is rather challenging, but a more reliable method for MCI detection. Comparison of both methods showed that MoCA detected the majority of MCI patients [8, 10, 15]. MoCA is highly sensitive when it comes to MCI detection, but specificity of MoCA is quite low, thus subjects with normal cognitive function might be falsely labeled with impaired cognition. Carotid stenosis detected in population older than 65 was 75 % for men and 62 % for women, with prevalence of stenosis ≥ 50 % in this population 7 % for men and 5 % for women [1, 16]. The indication for carotid endarterectomy (CEA) and carotid artery stenting (CAS) in asymptomatic patients remains a controversial issue which deserves a nuanced approach. Pivotal role of the best medical treatment has been elaborated in different professional guidelines with regard to this issue. In order to prevent potential stroke and disability, European Society of Cardiology (ESC) established widely used therapeutic strategies for the management of asymptomatic carotid artery disease. According to the recommendations, CEA should be considered in asymptomatic patients with carotid artery stenosis ≥ 60 %, as long as the perioperative stroke and death rate for procedures performed by the surgical team is < 3 % and the patient's life expectancy exceeds

5 years. In asymptomatic patients with an indication for carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centers with documented death or stroke rate < 3 % [17]. The European Stroke Initiative (EUSI) Executive Committee established widely used therapeutic strategies for carotid disease according to the results of large studies. According to this recommendations, patients suitable for CEA or CAS are those with stenosis > 70 % and without a severe neurological deficit with recent (< 180 days) ischemic events. These recommendations could be applied if the center's perioperative strokes and death rate is < 6 %. CAS or CEA may also be performed in patients with stenosis of 50–69 % free of severe neurological deficit only if the perioperative strokes and death rate is < 3 % [8–23]. According to the American recommendations for selection of patients for carotid revascularization based on Class I, selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy and other individual factors. These should include a thorough discussion of the risks and benefits of the procedure with an understanding for patient preferences. According to the Class IIa, it is reasonable to perform CEA in asymptomatic patients who have > 70 % stenosis of the ICA if the risk of perioperative stroke, MI, and death is low. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention. It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery. According to the Class IIb, prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60 % by angiography, 70 % by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established. In symptomatic or asymptomatic patients with high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, the effectiveness of revascularization versus medical therapy alone is not well established [33].

Patients and methods

There were 150 right-handed asymptomatic patients with severe ≥ 70 % unilateral ICA stenosis included in the study. There were no statistically significant differences between the number of males and females included in the study, and patients who were older than 65 years (80 males; mean age \pm SD, 67.2 \pm 15.3 years). The control group included 150 right-handed subjects (78 males; mean age \pm SD, 67 \pm 15.1 years) without carotid artery disease,

matched according to the demographic variables and vascular risk factors with the group of patients. All participants were right-handed with a dominant left hemisphere, thus the impact of a different dominant hemisphere was excluded during cognitive testing. Both patients and controls were assessed as right-handed by the Edinburgh Handedness Inventory [32]. Patient group was further divided according to the side of ICA stenosis, into left-sided or right-sided unilateral ICA stenosis subgroups. There were 76 patients with severe right-sided ICA stenosis, and 74 patients with severe left-sided ICA stenosis. All subjects signed an informed consent form approved by the hospital ethics committee. Subjects were asked about medical history, vascular risk factors, whereby patients with previous transient ischemic attack (TIA) or stroke, clinically evident coronary and/or peripheral artery disease and subjects with excessive alcohol consumption were excluded. Standard laboratory workup, blood pressure measurement, body mass index calculation and computed tomography (CT) brain scan, color Doppler flow imaging (CDFI) and power Doppler imaging (PDI) of extracranial arteries, TCD and BHI were performed. Subjects with normal CT brain scan or small intracranial vessels disease, without apparent territorial ischemic lesions, hemorrhage or brain tumors were also included in the study. Cognitive status was evaluated by means of MMSE and MoCA. Different MMSE categories were evaluated (orientation, registration, attention and calculation, recall and language) and total score of 25–30 was considered normal. MoCA categories (alternating trial making, visual–constructional skills, naming, and attention, sentence repetition, verbal fluency, and abstracting, immediate and delayed recall, orientation) were also evaluated and total MoCA score of 26–30 was regarded as normal. Ultrasound measurements were performed in a supine position with head elevated up to 45° and side tilt of 30° to the right and to the left. Evaluation of extracranial blood vessels was performed by CDFI and PDI method using Aloka 5500 Prosound, with 7.5 MHz linear probe in a standardized manner [15, 16]. Degree of stenosis was defined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [18]. TCD examination was performed using DWL Multidop X4 instrument with 2 MHz hand-held pulsed wave Doppler probe. Collateral intracranial circulation was evaluated by transcranial color coded doppler (TCCD), thus the mean blood flow velocity (MBFV) increase of 20 % from the baseline value without present signs of arterial diameter stenosis, was considered as intracranial collateral circulation [21–23]. Breath holding index (BHI) was calculated as a percentage increase of MBFV during breath holding and divided by the time, calculated in seconds, for which the subject held its breath [21–23]. Statistical analysis of different parameters which

Table 1 Prevalence of risk factors in patient and control group

Risk factors	Number of patients (%)	Number of controls (%)
Males/females	80/70 (53/47)	78/72 (52/48)
Age > 65 years	150	150
Hypertension	50 (33)	50 (33)
Atrial fibrillation	20 (13)	19 (13)
Diabetes mellitus	30 (20)	29 (19)
Hyperlipidemia	30 (20)	30 (20)
Smoking	10 (15)	10 (15)
Obesity	10 (15)	12 (8)
Multiple risk factors (>2)	78 (52)	75 (50)

included BHI values, MMSE and MoCA scores was performed by means of Student *t* test, and statistical significance was set at $p < 0.05$ value.

Results

There were 150 right-handed asymptomatic patients with severe ≥ 70 % unilateral internal carotid stenosis included in the study and 150 right-handed subjects without internal carotid stenosis, matched by demographics and vascular risk factors with the patient group. All subjects included in the study were right-handed thus the influence of different hemispheric dominance was diminished during cognitive testing. All patients were aged >65 years (mean \pm SD; 67.2 ± 15.3) and there was no significant difference between number of males and females included in the study. Most of the patients (52 %) had multiple vascular risk factors. Hypertension, diabetes mellitus and hyperlipidemia were the most frequent single vascular risk factors (Table 1). Patients and controls did not differ significantly in age, gender or proportion of vascular risk factors. MMSE scores did not significantly differ in patients and controls. Patients with severe unilateral ICA stenosis had MMSE scores within a normal range, but MoCA scores were lower than normal. BHI and MoCA values were significantly lower in all patients, but no significant changes of MMSE values were detected ($p > 0.05$) (Table 2). Patients with a single intracranial collateral artery recruited had slightly better cognitive results, than patients with two or more intracranial collateral arteries recruited (Table 3). Subgroups of patients with left and right ICA stenosis did not significantly differ in age, gender, vascular risk factors or cognitive scores. Overall BHI, MoCA and MMSE values were not significantly different, when compared to the side of ICA stenosis ($p > 0.05$). By examining the side of the observed stenosis, it has been noted that patients with severe left-sided ICA stenosis had lower MoCA scores in

Table 2 BHI, MMSE and MoCA scores, according to the number of recruited intracranial collateral arteries

Number of recruited collateral arteries	1	2	3	4	5
BHI*	0.95 ± 0.2	0.76 ± 0.4	0.69 ± 0.5	0.61 ± 0.5	0.56 ± 0.7
MMSE	28.1 ± 1.1	28.2 ± 0.9	28.0 ± 0.9	27.8 ± 1.4	27.9 ± 1.5
MoCA*	23.1 ± 1.1	22.8 ± 0.9	21.6 ± 1.2	20.4 ± 1.1	20.1 ± 1.1

Values are presented as mean ± standard deviation

* $p < 0.05$

Table 3 BHI, MMSE and MoCA scores, according to the recruitment of primary and secondary intracranial collateral pathways

	ACoA	PCoA	ACoA/PCoA	ACoA/OA	PCoA/OA	ACoA/PCoA/OA	Cortical arteries
BHI*	0.95 ± 0.2	0.90 ± 0.5	0.89 ± 0.4	0.72 ± 0.4	0.7 ± 0.5	0.59 ± 0.5	0.58 ± 0.7
MMSE	28.0 ± 0.6	28.0 ± 0.9	28.1 ± 0.8	28.2 ± 1.2	28.1 ± 1.1	27.8 ± 1.2	27.9 ± 1.3
MoCA*	23.2 ± 1.1	23.1 ± 1.0	23.0 ± 1.4	22.8 ± 1.2	22.1 ± 0.9	21.7 ± 1.2	20.0 ± 0.9

Values are presented as mean ± standard deviation

* $p < 0.05$

categories of language and episodic memory performance, while subjects with severe right-sided ICA stenosis had lower MoCA scores in a category of visual–spatial skills (Table 4).

Discussion

Most patients with cognitive decline and carotid stenosis have multiple vascular risk factors, as documented in previous studies [9, 26]. Assessment of cognitive decline showed that MMSE is not quite an adequate method for MCI recognition, which is in agreement with the results of our study. In patients with primary intracranial collateral pathways, ophthalmic artery and cortical collaterals

activated, overall MoCA and BHI values were lower, but according to different MoCA categories there were significantly higher scores of visual–spatial and executive skills in patients with left-sided ICA stenosis, and significantly higher scores in language and delayed recall categories in patients with right-sided ICA stenosis. Results of our study showed that altered cerebrovascular reactivity appears to be linked to side-specific cognitive functionality. Results of this study are comparable with previous studies which suggested that decreased cerebral autoregulation might be utilized in recognizing patients with increased risk for MCI [27, 28]. Intracranial collateral flow via the ophthalmic artery and flow via leptomeningeal vessels have been considered secondary collaterals, which are recruited only if the primary collateral circulation via the circle of Willis is insufficient. Patients with severe asymptomatic ICA stenosis with collateral circulation through the ophthalmic artery or through leptomeningeal vessels in addition to collaterals via the circle of Willis have a worse hemodynamic status of the brain than those with Willisian collaterals only. Therefore, the presence of these collaterals may indicate insufficiency of collateral blood flow via the circle of Willis [28–31]. Results of our study also showed that alteration of cerebrovascular autoregulation might be responsible for specific cognitive function decline. Furthermore, our study proved that BHI and MoCA were adequate methods for MCI detection in asymptomatic patients with severe ICA stenosis. Limitations of this study include the drawback of using only MMSE and MoCA for neuropsychological assessment and the lack of other more sophisticated neuroimaging data for comparison with the ultrasound data, for instance computed tomography angiography or magnetic resonance angiography of the carotid arteries and intracranial arteries,

Table 4 BHI, MMSE and different MoCA categories scores, evaluated according to the side of ICA stenosis

	Left ICA stenosis	Right ICA stenosis
BHI	0.61 ± 0.32	0.56 ± 0.41
MMSE	28.3 ± 2.1	28.5 ± 1.8
MoCA	21.8 ± 2.1	22.1 ± 1.9
Attention	4.9 ± 0.4	4.8 ± 0.6
Naming	2.4 ± 0.5	2.6 ± 0.4
visual–spatial/executive	3.6 ± 1.2*	2.1 ± 1.1*
Language	1.4 ± 0.5	2.3 ± 0.6*
Abstraction	1.6 ± 0.3	1.8 ± 0.2
Delayed recall	2.1 ± 0.8	3.4 ± 0.9*
Orientation	4.9 ± 0.4	4.5 ± 0.5

Values are presented as mean ± standard deviation

ICA internal carotid artery

* $p < 0.05$

or magnetic resonance imaging to assess silent infarctions or micro-hemorrhages in more detail. Most of the studies which evaluated cognitive functions before and after CEA or CAS have shown that there is improvement or status quo in cognitive functions, but no deteriorations. Meta-analysis of 28 studies has shown improvement in cognition after CEA in the most of studies. In minority of these studies there was no change in cognition detected and results of a single study showed cognitive deterioration. Statistically significant results were found in tests of verbal fluency and memory. Studies evaluating impact of CEA on cognitive decline in patients with symptomatic and asymptomatic carotid stenosis have shown that approximately 80 % of patients exhibited a decline in one or more test scores, while 60 % had one or more improved test scores at the time of the discharge from the hospital. The percentage of declined test scores was lower and that of improved test scores was higher in the follow-up examinations at 1 and 5 months. A decline in performance was seen most commonly in the verbal memory tests, whereas an improved performance was observed most frequently in the executive and motor tests [24, 25]. Some studies have reported an improved performance following CAS, whereas other authors concluded that, although there had been no significant change in most patients, an improvement or decline may be expected in individual cognitive domains. A further investigation in which the cognitive effects of CEA and CAS were compared in symptomatic cases demonstrated similar magnitudes of changes in both directions—improvement and decline, in the two groups following the procedures. Improvement in cognitive functioning following CEA or CAS may be expected from the reduced embolism and improved hemodynamics. Deterioration in cognition may result from perioperative impairment in perfusion pressure or procedure-related showers of emboli released into the cerebral circulation. Despite a probably higher rate of procedural embolizations, endovascular management has not generally been associated with extensive cognitive deterioration than in the case of CEA. With regard to the role of hemodynamic factors, longer cross-clamp times during CEA have been associated with a higher incidence of a cognitive dysfunction [24, 25]. Five-year follow-up study has not shown differences in mean MMSE scores in patients with asymptomatic stenosis receiving medical therapy vs. CEA [24, 25]. Substantially fewer data are available concerning the cognitive outcome of CAS. The improvement in cognitive function following carotid reconstruction may be greater in patients with low flow-endangered brains than in those with hemodynamically insignificant stenoses [24, 25]. There are still no clear recommendations about using CEA or CAS in treating cognitive deficit in otherwise asymptomatic patients, but it is important to recognize cognitive changes as a symptom

of ICA disease in order to follow-up with such patients and include cognitive deficit in perioperative risk calculation and benefit from CEA or CAS. In order to prevent further cognitive decline in patients with severe ICA disease, perioperative risk assessment of possible benefit from CEA or CAS should be patient-oriented, with an understanding of individual preferences, comorbid conditions and life expectancy, which might be considered as an argument for a more liberal surgical or endovascular approach, with consideration for patient preferences, only when conservative medical treatment has failed.

Conflict of interest None.

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