



Carotid stenosis and the cognitive function

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ABSTRACT

While stroke is a known cause of a cognitive impairment, the relationship between a carotid artery stenosis and the cognitive function in individuals without a history of stroke is less clear. A number of risk factors for vascular disease are related to a cognitive impairment. Hypertension, diabetes mellitus, cigarette smoking, and dyslipidemia are also associated with an increased risk of carotid artery disease. Some studies have suggested that a stenosis of the internal carotid artery may be an independent risk factor for a cognitive impairment. A high-grade stenosis of the internal carotid artery may be associated with a cognitive impairment even without evidence of infarction on magnetic resonance imaging. On the other hand, it is fairly common that patients display a normal cognition despite severe carotid artery disease, highlighting the important role of an efficient collateral blood supply. The possible pathomechanisms of a cognitive impairment include silent embolization and hypoperfusion. Carotid endarterectomy or stenting may lead to a decline in the cognitive function in consequence of microembolic ischemia or intraprocedural hypoperfusion. Conversely, perfusion restoration could improve a cognitive dysfunction that might have occurred from a state of chronic hypoperfusion. It is unclear whether these complex interactions ultimately result in a net improvement or a deterioration of the cognitive function. The evidence available at present does not seem strong enough to include consideration of a loss of cognition as a factor in determining the balance of the risks and benefits of therapy for a carotid stenosis.

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1. Introduction

A detectable carotid stenosis is present in 75% of men and 62% of women aged ≥ 65 years, the prevalence of a $\geq 50\%$ stenosis in this population being 7% in men and 5% in women [1]. Carotid occlusive disease is responsible for 15–20% of all ischemic strokes [2]. When evaluated with a standard neurological examination, however, a majority of carotid stenoses are asymptomatic, i.e. the patient has not experienced an episode of a retinal or a focal cerebral dysfunction in the territory of the affected internal carotid artery. The cognitive function is not taken into consideration when the symptomatic or asymptomatic status of a carotid artery is determined. Whereas stroke is a well-known cause of dementia [3], carotid stenosis itself is a less well-established independent risk factor for a cognitive impairment. The mechanisms of cognitive impairments occurring in patients with asymptomatic carotid stenosis are poorly understood.

Carotid endarterectomy (CEA) or carotid artery stenting (CAS) is frequently utilized for the treatment of carotid stenoses, with the main aim of preventing a future stroke [4–6]. These procedures may also influence the cognitive function, but the published data are conflicting

as to the direction of this cognitive change [7,8]. The exact mechanisms whereby a cognitive improvement or worsening may occur in association with carotid interventions likewise largely remain unidentified. It is unclear whether a cognitive assessment may facilitate decisions relating to the treatment of carotid stenosis.

The purpose of this review is to summarize available knowledge on the risk and possible pathomechanisms of cognitive impairment in patients with carotid stenosis, and on the influence of carotid interventions on cognitive functioning.

2. Assessment of cognitive function

In classical neurology, the term neurologic deficit relates to the loss of motor and sensory functions. However, mapping of the anatomical background of the impairment may be facilitated by examination of the cognitive functions. The term cognitive deficit refers to the loss of one or more cognitive functions. The various cognitive functions are connected with different neural networks/anatomical regions in the brain. Modern cognitive neuropsychology in conjunction with cognitive psychology and cognitive neuroscience has devised sophisticated methods with which to assess the different cognitive functions, thereby promoting the neurological diagnosis and a deeper understanding of the impairment or disease.

In clinical practice, the Mini-Mental State Examination (MMSE) [9] still remains the most commonly applied screening tool. The MMSE is

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Table 1
Examples of cognitive domains and tasks.

Domain	Task	Localization
Executive functions [10–15]	Verbal Fluency Task	Frontostriatal circuits
	Wisconsin Card Sorting Test (WCST)	
	STROOP	
	Digit Span Task	
Verbal short-term memory [16]	Word Recall Task	Broca's area
	Non-Word Repetition	Supplementary motor cortex
	Corsi Block-Tapping Test	Left posterior parietal cortex
Visuo-spatial short-term memory [17]	Visual Pattern Span Task	Right posterior parietal cortex
	Reading Span Task	Dorsolateral prefrontal cortex
Listening Span Task		
Complex working memory [18,19]	Counting Span Task	
	Operation Span	
	Backward Digit Span	
	Rivermead Behavioral Memory Test (RBMT)	Medial temporal lobe
Delayed Recall Tasks		
Episodic memory [20]	The Serial Reaction Time Task (SRTT)	Basal ganglia
	Weather Prediction Task	Cerebellum
	Artificial Grammar Learning	

a brief composite measure of the mental status (with a maximum score of 30, or in newer versions 100); despite the several deficiencies of this method, this is the index most frequently used to stratify the severity of a cognitive impairment and dementia. The main problem with the MMSE is that it is unable to differentiate between cognitive functions, and is therefore of little value for a deeper neuropsychological diagnosis and a more fundamental analysis.

Modern neuropsychology makes use of separate tasks to assess the various cognitive functions, which are controlled by different brain regions. The neuropsychological tests are designed to test individual domains. The neuroanatomical background of these tasks was investigated by different methods, including brain imaging (fMRI, PET), event-related potential and neuropsychological methods (lesion studies). During the last 10 years, consensus has emerged in this field in that the traditional neuropsychological domains (such as attention, learning, memory, language, problem-solving and thinking) are too broad, not consistently defined, and difficult to link to specific brain circuits. It is better to use well-defined, more discrete cognitive functions or specific processes, e.g. phonological short-term memory, spatial short-term memory, verbal working memory, episodic memory, mental lexicon, lexical access, executive function, implicit learning, etc., which are related to specific neuronal systems. Some examples of the neuropsychological domains and tasks are presented in Table 1. The cognitive tests listed here are not necessarily those used in the studies referred to elsewhere in this paper.

3. Carotid stenosis and risk of cognitive impairment

A systematic review of 18 studies addressing the issue of cognitive function and symptomatic or asymptomatic carotid occlusive disease in patients who have not (yet) undergone surgery found that 14 had reported cognitive deficits [24]. However, the patient characteristics, study design, neuropsychological assessment procedures and interpretations varied widely from study to study. Furthermore, a majority of the studies did not report on the occurrence of vascular risk factors or on cerebral imaging results.

Conventional vascular risk factors (hypertension, diabetes, dyslipidemia and smoking) are risk conditions for stroke, carotid stenosis and dementia alike [1,3]. Theoretically, a carotid stenosis may be a direct cause of a reduced level of cognitive functioning, or it may act only as a marker of intracerebral or generalized atherosclerosis. The

presence of ischemic brain injury in patients with a symptomatic stenosis may easily explain any cognitive impairment observed in such cases. It is less clear whether an asymptomatic carotid stenosis itself (i.e. in the absence of stroke symptoms) is an independent risk factor for a cognitive impairment (Fig. 1). The relationship of an asymptomatic stenosis with a cognitive impairment is discussed below.

Mathiesen et al. reported the observations from the Tromsø study [25]. Only individuals without a previous history of stroke were included in the analysis. Carotid stenoses were measured by means of ultrasonography, and an MRI of the brain was also carried out. Most of the participants in the carotid stenosis group had right-sided or bilateral narrowings of $\geq 35\%$. The mean age was around 68 years. The individuals in the age- and sex-matched control group did not exhibit carotid stenoses. The performances in a battery of extensive neuropsychological tests were compared in the subjects with and without carotid stenoses. The study demonstrated that the subjects with carotid stenoses achieved significantly lower levels of performance in several subsets of cognitive tests. This association was independent of the presence of brain MRI lesions. Moreover, some of the neuropsychological tests revealed a graded relationship to the degree of stenosis.

Johnston et al. evaluated the individuals participating in the Cardiovascular Health Study [26]. 4006 right-handed men and women ≥ 65 years of age, without a history of stroke, transient ischemic attack (TIA) or CEA were included in the study. Internal carotid artery stenoses were measured by duplex ultrasonography. A brain MRI was also performed. The modified MMSE was used for cognitive assessment. A cognitive impairment was defined as a score of <80 of a possible 100 points. This set of tests primarily measures the cognitive function in the dominant cerebral hemisphere, which is the left hemisphere in $>98\%$ of right-handed persons. The study found that a high-grade ($\geq 75\%$) stenosis of the left internal carotid artery was associated with a cognitive impairment and cognitive decline during the follow-up. No such significant correlation was observed for right-sided stenoses. The association persisted after adjustment for right-sided disease and for vascular risk factors, which indicates that it was not due to underlying vascular risk conditions or atherosclerosis in general. The correlation of a left carotid stenosis with a cognitive impairment was observed even in participants without evidence of cerebral infarction on MRI. The above observations support the idea that an asymptomatic carotid stenosis may be an independent risk factor for a cognitive impairment and decline.

4. Pathomechanism of cognitive impairment in carotid stenosis

A silent brain infarction may be an intermediate between a carotid stenosis and a cognitive impairment. Lacunar infarcts have been reported to be more frequent in patients with asymptomatic carotid stenoses as compared with controls [25]. CT has been stated to reveal a silent infarction in 15–19% of patients with asymptomatic stenoses [27,28]. A more frequent occurrence of lesions on the side of the study

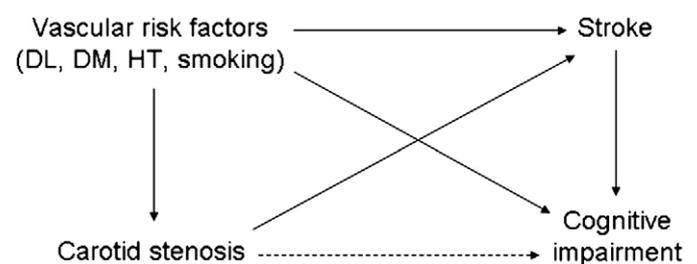


Fig. 1. Interdependence of vascular risk factors, stroke, carotid stenosis and cognitive impairment. See text for explanation. DL, dyslipidemia, DM, diabetes mellitus, HT, hypertension.

artery has been reported by some investigators [27], but an even distribution between the ipsi- and contralateral sides has been observed by others [28]. The MRI presence of silent brain infarcts in the general population has been concluded to increase the risk of dementia, and subjects with silent infarcts displayed a steeper decline in cognitive function than those without silent infarcts [29]. Interestingly, not only silent infarctions, but also white matter changes may play a role. A graded relationship has been detected between the numbers of carotid plaques and periventricular white matter lesions [30]. There is evidence that white matter lesions are involved in the pathogenesis of a cognitive impairment [31].

The two important mechanisms implicated in a carotid stenosis-related cognitive impairment, either with or without the presence of a silent brain infarction, are embolization and hypoperfusion. A recent study indicated that spontaneous cerebral emboli, as detected by a 1-hour transcranial Doppler monitoring of the middle cerebral artery, were significantly more frequent in patients with both Alzheimer's disease and vascular dementia than in the controls [32]. Although a significant association between severe carotid disease and spontaneous cerebral emboli was observed only among the controls, and not in the demented patients, this study still highlights the potential pathogenic role of cerebral embolization in a cognitive impairment. Spontaneous cerebral emboli are also associated with an accelerated decline in cognition in demented patients [33]. However, in a cohort of older people, the cognitive decline was not associated with asymptomatic spontaneous cerebral embolization, but rather with higher age, a history of stroke and the presence of carotid stenosis [34]. Arguments against embolization as the main mechanism of the cognitive impairment in carotid stenosis include the observations from the Tromsø Study [25] and the Cardiovascular Health Study [26], where the cognitive impairment in the patients with carotid stenoses was independent of the vascular lesions revealed by MRI. However, microembolization does not necessarily lead to MRI lesions.

Brain hypoperfusion may be a consequence of a carotid stenosis [35]. Furthermore, certain evidence suggests that cerebral hypoperfusion may contribute to the onset of clinical dementia [36]. The graded relationship of a cognitive impairment to the degree of carotid stenosis observed in the Tromsø Study could support the role of a hemodynamic compromise, but the degree of stenosis was low in most patients, not reaching the level of hemodynamic significance [25]. The possible pathogenic role of hypoperfusion in a cognitive impairment was also suggested by two studies of patients with heart failure [37,38], a condition characterized by impaired hemodynamics.

5. Carotid interventions and cognitive function

Several studies have demonstrated an improvement, others no change, and still others a decline in neuropsychological performance following CEA. A systematic review of 28 studies on the impact of CEA upon the cognitive functioning [7] found that a majority (16) of the papers reported an improvement in cognition after surgery, while a substantial minority (11) detected no change, and a deterioration was observed in one investigation. Some benefit from surgery was commonly revealed by tests of verbal fluency and memory. A cognitive improvement was the more likely, the longer the time interval between CEA and assessment. Given the conflicting findings and the differences in many methodological factors in the various studies, it was not possible to draw any clear-cut conclusion regarding the impact of CEA upon cognition.

In a 5-year follow-up study of 1659 patients with asymptomatic carotid stenoses, there was no difference in mean MMSE scores between those receiving medical therapy and those undergoing CEA [39]. There was a gradual decline in the mean scores over time, but this trend was not significant and occurred at the same rate in each group.

Heyer et al. utilized a battery of neuropsychological tests to evaluate 120 patients undergoing CEA for symptomatic or asymptomatic

stenosis, and found that approximately 80% of them exhibited a decline in one or more test scores, while 60% had one or more improved test scores at hospital discharge [40]. The percentage of declined test scores was lower and that of improved test scores 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. Another study by the same group indicated that the cognitive decline following CEA was unrelated to the general anesthesia [41]. Predictors of a neurocognitive decline after CEA include advanced age, diabetes, obesity, the preoperative monocyte count and the presence of the APOE-ε4 allele [42–44].

Substantially fewer data are available concerning the cognitive outcome of CAS. Some studies have reported an improved performance following CAS [45,46], whereas the authors of another investigation concluded that, although there had been no significant change in most patients, an improvement or decline may be expected in individual neurocognitive domains [47]. A further investigation in which the cognitive effects of CEA and CAS were compared in symptomatic cases demonstrated similar magnitudes of changes (both in improvement and in worsening) in the two groups following the procedures [8].

As concerns the mechanisms involved in the cognitive changes associated with carotid interventions, an improvement in cognitive functioning following CEA or CAS may be expected from the reduced embolism and the improved hemodynamics. Alternatively, a deterioration in cognition may result from a perioperative impairment in perfusion pressure or procedure-related showers of emboli released into the cerebral circulation. Declines in cognitive function after CEA have been associated with elevations of the serum level of protein S100B, a marker of glial cell death, indicating the occurrence of cerebral injury [48]. Neuropsychological deficits after routine cardiopulmonary bypass appeared to be related to the number of microemboli delivered during surgery [49]. Intraoperative embolization during CEA, as detected by transcranial Doppler, was reported to be correlated with the postoperative cognitive deterioration [50]. Interestingly, another study of patients undergoing CEA or CAS did not indicate any correlation between the inferior cognitive outcome and transcranial Doppler-detected procedural embolization or ischemia, though the case numbers were relatively low [51]. Despite a probably higher rate of procedural embolization [52,53], endovascular management has not generally been associated with a more extensive cognitive deterioration than in the case of CEA [8,51]. As regards the role of hemodynamic factors, longer cross-clamp times during CEA have been associated with a higher incidence of a cognitive dysfunction [54]. 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 [55,56].

6. Conclusion

A carotid artery stenosis appears to be an independent risk factor for a cognitive impairment. The main mechanisms that lead to deficits in cognitive functioning are embolization and hypoperfusion. Carotid interventions may leave the neuropsychological performance unchanged, or may result in a decline or an improvement. CAS may not be different from CEA from the aspect of the cognitive outcome. There is no evidence to support the performance of prophylactic CEA or CAS with the aim of preventing a cognitive decline in otherwise asymptomatic patients.

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