

**REVIEW**

**DERLEME**

**THE EFFECT OF ASYMPTOMATIC CAROTID ARTERY STENOSIS ON COGNITIVE FUNCTIONS**

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**ABSTRACT**

Both cerebrovascular diseases and dementia are important clinical conditions that disrupt daily life and mental abilities. Carotid artery stenosis is the cause of 10-15% of ischemic strokes. Symptomatic and asymptomatic carotid artery stenosis is a little-known, but important risk factor in the etiology of all causes of dementia, including both mild cognitive impairment and Alzheimer's disease. In this review, the effect of asymptomatic carotid artery stenosis on cognition is discussed.

**Key Words:** Carotid artery stenosis, cognition, dementia, asymptomatic.

**ASEMPTOMATİK KAROTİS ARTER DARLIĞININ KOGNİTİF FONKSİYONLARA ETKİSİ**

**ÖZET**

Hem serebrovasküler hastalıklar hem demans günlük yaşamı ve zihinsel yetileri bozan önemli klinik durumlardır. Karotis arter darlığı iskemik inmelerin %10-15'inin nedenidir. Hem hafif kognitif bozukluk hem de Alzheimer Hastalığını da dahil olmak üzere tüm demans nedenlerinin etyolojisinde semptomatik ve asemptomatik karotis arter darlığı az bilinen ama önemli bir risk faktörüdür. Bu derlemede asemptomatik karotis darlığının kognisyona olan etkisinin tartışılması amaçlanmaktadır.

**Anahtar Sözcükler:** Carotid artery stenosis, cognition, dementia, asymptomatic.

**INTRODUCTION**

Asymptomatic carotid artery stenosis (CAS) is one of the most important risk factors for ischemic stroke. The effect of vascular risk factors in the development and progression of cognitive disorders, such as mild cognitive impairment and dementia, is one of the major topics studied in recent years. In this review, the effect of asymptomatic carotid artery stenosis on cognition is discussed.

**Epidemiology**

Approximately 85% of all strokes are ischemic. Carotid artery stenosis is the reason for 10-15% of ischemic strokes (1, 2). The risk of stroke is known to increase as the degree of CAS increases (3). CAS is present in 8-13% of patients admitted with transient ischemic attack (4).

The importance of identifying and rating CAS has been demonstrated by the NASCET (the North American Symptomatic Carotid Endarterectomy

Trial), ECST (the European Carotid Surgery Trial) and ACAS (the Asymptomatic Carotid Atherosclerosis Study) studies (5-7). Hypertension, lipid metabolism disorders, sedentary lifestyle, and diabetes are the most common risk factors of CAS. Lesions of CAS that do not cause stroke symptoms are defined as 'asymptomatic'. In prevalence studies, asymptomatic CAS was found as approximately 4.2-6%. Its prevalence is 12.5% in men, and 6.9% in women over the age of 70 (8,9). In 6% of patients with primary asymptomatic CAS, minor ischemic events, such as transient ischemic attacks are observed. The damages that asymptomatic CAS can cause in the brain structure and especially in cognitive functions are still debatable.

Dementia is defined as an impairment that affects daily life in cognitive areas, such as language, attention, executive functions, and praxia, without brain fog. Mild cognitive impairment (MCI) is a cognitive impairment that does not affect daily life activities (10).

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The prevalence of dementia is 5-10% over the age of 65, and it is known to be doubled each decade. One in three individuals over the age of 80 have symptoms of dementia (10). The prevalence of dementia in the world is projected to double by 2030 and triple by 2050 (11). One of the major public health problems is Alzheimer's disease, which is most common among cognitive disorders. The prevalence of MCI varies between 5% and 36.7% in the studies, and the variability of the neurocognitive battery used in the diagnosis is believed to be the cause of the variability in the prevalence (12).

### **A Brief Overview of Carotid Artery Atherosclerosis**

Increased Intima media thickness and atherosclerotic plaques lead to loss of homogeneity of the carotid artery and changes in arterial blood flow. Carotid artery bifurcation and proximal internal carotid artery are the most common areas in atherosclerotic carotid artery disease. The increase in atherosclerotic plaques causes contractions in the lumen. Ischemic stroke or transient ischemic attacks occur by thromboembolic and hemodynamic mechanisms. Ulceration on atherosclerotic plaque surface, plaque size, extent of stenosis and intra-plaque hemorrhage are decisive in the formation of neurological symptoms (13).

### **Carotid Artery Stenosis and Cognitive Disorders**

CAS is among the well-known causes of atheroembolic stroke. Cognitive impairment, however, may be associated with stroke or vascular risk factors, such as diabetes, hypertension, and hyperlipidemia (9). Vascular dementia (VaD) is a clinical manifestation that develops after a stroke due to brain damage and loss of cognitive function. All causes of ischemic and hemorrhagic stroke can cause VaD. VaD is the second most common cause of dementia following Alzheimer's disease (14).

Vascular cognitive impairment (VCI) was defined by Bowler and Hachinski as a clinical condition can include all levels of cognitive impairment, which may occur due to all causes of cerebrovascular disease, from the earliest stages (15). The potential mechanism of vascular cognitive impairment is believed to be

microembolus in unstable carotid plaques and cerebral hemodynamic insufficiency (9).

There are many studies investigating the relationship between carotid artery diseases and cognitive disorders (16,17). Many studies have shown that both symptomatic and asymptomatic CAS leads to worsening in cognitive tests, compared to healthy volunteers (9, 18-21).

In a study conducted by Johnston et al. of 4006 patients over 65 years of age, the presence of plaque, intima-media thickness and luminal stenosis were evaluated by Doppler ultrasound in both carotid arteries. Cognitive changes were examined by the mini-mental state examination (MMSE) test. Cognitive impairment was significantly higher in asymptomatic patients, especially with advanced stenosis ( $\geq 75\%$ ) in the left carotid artery (22).

In another study, Wei et al. also found more frequent cognitive impairment in acute ischemic stroke patients and in patients with advanced CAS (23).

In another study, 91 female patients over the age of 60 were followed for 12 years, and the carotid artery intima-media thickness was shown to be an independent risk factor for impaired memory function (24).

In a functional MRI study by Wang et al., asymptomatic CAS patients were investigated and found to be significantly behind in global cognition, memory and functionality compared to the control group (18). Wendell et al. followed 364 patients over the age of 60 for 14 years and showed that CAS is a prospective risk factor for dementia (11). They reported that CAS increased the risk of dementia and Alzheimer's disease by 2-2.5 fold, when age, race, gender, education level, high blood pressure, high cholesterol, coronary artery disease, diabetes and smoking risk factors were adjusted. In a population study with 210 patients, patients with asymptomatic carotid stenosis over the age of 60 were evaluated, and cognitive function impairment was detected in the presence of plaque in the carotid (25). It was also shown that patients with carotid stenosis above 75% scored lower on the MMSE test (16).

Carotid artery stenosis has been reported to cause a decrease in ipsilateral cortical thickness and progressive brain atrophy in follow-up (26, 27). There are also studies showing that cognitive tests, including attention, memory and language tests, deteriorate with decreased cortical thickness

(28,29). It is also believed that white matter lesions may be correlated with cognitive deterioration (30). Nickel et al. compared 25 patients with unilateral asymptomatic carotid stenosis without ischemic brain lesions with 25 healthy controls in terms of cortical thickness and cognitive abilities, and found no difference between cortical thickness, but found deterioration in cognitive tests (dementia screening test, clock drawing and tracking test) in the patient group (8).

Cognitive impairment was associated with cerebral hypoperfusion, and etiological studies showed that glutamate excitotoxicity and progressive death of neurons are part of neurodegeneration (25,31). Even without distinct infarction, global cerebral hypoperfusion can cause ischemic damage and cause cognitive impairment (32). Inadequate collateral circulation is also believed to have an effect on cognitive loss (8).

Cardiovascular risk factors play an important role both in the etiology of all causes of dementia, including MCI and Alzheimer's disease, as well as in the etiology of CAS patients (11,33,34). In the evaluation of all stroke patients and transient ischemic attack patients, it is important to investigate the risk factors as well as questioning the cognitive loss. Some studies, however, have reported that patients with asymptomatic CAS develop vascular cognitive impairment, regardless of vascular risk factors. The underlying mechanism has been explained as the hypoperfusion due to insufficient collateral circulation, and hemodynamic insufficiency due to decreased cerebrovascular reserve (9).

### Evaluation of Cognitive Status

Many methods are used for the evaluation of cognitive impairment. It is quite important to question the impact of cognitive loss on daily life. Although the mini-mental state examination (MMSE) is the most commonly used cognitive assessment test, it is insufficient for the diagnosis and assessment of dementia, MCI and delirium. However, it is still up to date since it is a good and a quick screening test, screens multiple cognitive sites and gives an idea about whether to perform

further tests (35). Most of the neuropsychological tests used to evaluate cognitive status examine verbal and non-verbal memory, attention and concentration, motor skills, reasoning, executive functions, and visuospatial functions (9). Diseases that can affect cognition, such as depression and anxiety disorder, should also be considered.

### Evaluation of Carotid Artery Disease

Asymptomatic CAS is rare compared to symptomatic patients. It is detected by chance or based on a murmur heard in the neck. It can be evaluated by non-invasive imaging methods, such as carotid artery Doppler ultrasound (USG), computed tomography angiography (CTA), and magnetic resonance angiography (MRA) [36]. However, conventional digital substrate angiography (DSA) is still the gold standard diagnostic method, despite having a 0.1-0.5% risk of stroke during the procedure (37).

In addition to medical treatment in patients with advanced CAS, there are treatment options including carotid balloon angioplasty, carotid artery stenting (CS) and carotid endarterectomy (CEA). Treatment preference for CAS patients is based on comorbid conditions, such as the presence of neurological symptoms, degree of stenosis, vascular and local anatomical features. Revascularization decisions should be made on a case-basis by a multidisciplinary team with a vascular neurologist.

Although CEA is the first choice, carotid artery stenting is also considered an appropriate alternative treatment method with similar efficacy and complication rates (36). The carotid artery stenting is particularly preferable in patients at high risk and has been found to be as effective and safe as endarterectomy (38).

### CONCLUSION

Both cerebrovascular diseases and dementia are important clinical conditions as they impair daily life and mental abilities. In asymptomatic carotid stenosis patients with impaired cognitive functions, identifying and preventing the risk factors, diagnosing early and treating with appropriate treatment will prevent cognitive impairment that leads to loss of functionality.

## REFERENCES

1. Cui L, Han Y, Zhang S, Liu X and Zhang J. Safety of stenting and endarterectomy for asymptomatic carotid artery stenosis: a meta-analysis of randomised controlled trials. *European Journal of Vascular and Endovascular Surgery* 2018; 55: 614-24.
2. White CJ. Carotid artery stenting. *Journal of the American college of Cardiology* 2014; 64: 722-31.
3. Gaba K, Ringleb PA and Halliday A. Asymptomatic Carotid Stenosis: Intervention or Best Medical Therapy? *Current neurology and neuroscience reports* 2018; 18: 80.
4. Coutts SB, Simon JE, Eliasziw M, et al. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* 2005; 57: 848-54.
5. Collaborators\* NASCET. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *New England Journal of Medicine* 1991; 325: 445-53.
6. Group ECSTC. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet*. 1991; 337: 1235-43.
7. Collaborators A. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995; 273: 1421-8.
8. Nickel A, Kessner S, Niebuhr A, et al. Cortical thickness and cognitive performance in asymptomatic unilateral carotid artery stenosis. *BMC cardiovascular disorders* 2019; 19: 154.
9. Lal BK, Dux MC, Sikdar S, et al. Asymptomatic carotid stenosis is associated with cognitive impairment. *Journal of vascular surgery* 2017; 66: 1083-92.
10. Wimo A, Jönsson L, Bond J, Prince M, Winblad B and International AD. The worldwide economic impact of dementia 2010. *Alzheimer's & Dementia* 2013; 9: 1-11. e3.
11. Wendell CR, Waldstein SR, Ferrucci L, O'Brien RJ, Strait JB and Zonderman AB. Carotid atherosclerosis and prospective risk of dementia. *Stroke* 2012; 43: 3319-24.
12. Sachdev PS, Lipnicki DM, Kochan NA, et al. The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: the COSMIC collaboration. *PloS one* 2015; 10: e0142388.
13. Carr S, Farb A, Pearce WH, Virmani R and Yao JS. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. *Journal of vascular surgery* 1996; 23: 755-66.
14. Rocca WA, Hofman A, Brayne C, et al. The prevalence of vascular dementia in Europe: facts and fragments from 1980-1990 studies. *Annals of neurology* 1991; 30: 817-24.
15. Bowler JV. The concept of vascular cognitive impairment. *Journal of the Neurological Sciences* 2002; 203: 11-5.
16. Ahmadi R, Willfort A, Lang W, et al. Carotid artery stenting: effect of learning curve and intermediate-term morphological outcome. *Journal of Endovascular Therapy* 2001; 8: 539-46.
17. Mlekusch W, Schillinger M, Sabeti S, et al. Hypotension and bradycardia after elective carotid stenting: frequency and risk factors. *Journal of Endovascular Therapy* 2003; 10: 851-9.
18. Wang T, Xiao F, Wu G, et al. Impairments in brain perfusion, metabolites, functional connectivity, and cognition in severe asymptomatic carotid stenosis patients: an integrated MRI study. *Neural plasticity* 2017; 2017.
19. Norling AM, Marshall RS, Pavol MA, et al. Is Hemispheric Hypoperfusion a Treatable Cause of Cognitive Impairment? *Current cardiology reports* 2019; 21: 4.
20. Alhusaini S, Karama S, Nguyen TV, et al. Association between carotid atheroma and cerebral cortex structure at age 73 years. *Annals of neurology* 2018; 84: 576-87.
21. Jackson DC, Sandoval-Garcia C, Rocque BG, et al. Cognitive deficits in symptomatic and asymptomatic carotid endarterectomy surgical candidates. *Archives of Clinical Neuropsychology* 2015; 31: 1-7.
22. Johnston SC, O'Meara ES, Manolio TA, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. *Annals of internal medicine* 2004; 140: 237-47.
23. Yue W, Wang A, Zhu R, et al. Association between carotid artery stenosis and cognitive impairment in stroke patients: a cross-sectional study. *PloS one* 2016; 11: e0146890.
24. Komulainen P, Kivipelto M, Lakka TA, et al. Carotid intima-media thickness and cognitive function in elderly women: a population-based study. *Neuroepidemiology* 2007; 28: 207-13.
25. Mworozzi K, Ameda F, Byanyima RK and Nakasujja N. Carotid artery plaque detected on ultrasound is associated with impaired cognitive state in the elderly: A population-based study in Wakiso district, Uganda. *Journal of Clinical Neuroscience* 2019.
26. Marshall RS, Asllani I, Pavol MA, Cheung Y-K and Lazar RM. Altered cerebral hemodynamics and cortical thinning in asymptomatic carotid artery stenosis. *PloS one* 2017; 12: e0189727.
27. Avelar WM, D'Abreu A, Coan AC, et al. Asymptomatic carotid stenosis is associated with gray and white matter damage. *International Journal of Stroke* 2015; 10: 1197-203.
28. Kim H, Ye B, Yoon C, et al. Cortical thickness and hippocampal shape in pure vascular mild cognitive impairment and dementia of subcortical type. *European journal of neurology* 2014; 21: 744-51.
29. Muller M, Appelman AP, van der Graaf Y, Vincken KL, Willem PTM and Geerlings MI. Brain atrophy and cognition: interaction with cerebrovascular pathology? *Neurobiology of aging* 2011; 32: 885-93.
30. Fischl B, Sereno MI, Tootell RB and Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human brain mapping* 1999; 8: 272-84.
31. Relja M. Pathophysiology and classification of neurodegenerative diseases. *EJIFCC* 2004; 15: 97.
32. Román GC. Brain hypoperfusion: a critical factor in vascular dementia. *Neurological research* 2004; 26: 454-8.
33. Kaffashian S, Dugravot A, Brunner EJ, et al. Midlife stroke risk and cognitive decline: a 10-year follow-up of the Whitehall II cohort study. *Alzheimer's & Dementia* 2013; 9: 572-9.
34. Hazzouri AZA, Haan MN, Neuhaus JM, et al. Cardiovascular Risk Score, Cognitive Decline, and Dementia in Older Mexican Americans: The Role of Sex and Education. *Journal of the American Heart Association* 2013; 2: e004978.
35. Mitchell AJ. The Mini-Mental State Examination (MMSE): update on its diagnostic accuracy and clinical utility for cognitive disorders. *Cognitive Screening Instruments*. Springer 2017, p. 37-48.

36. Naylor A, Ricco J-B, De Borst G, et al. Editor's choice-management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *European Journal of Vascular and Endovascular Surgery* 2018; 55: 3-81.
37. Dharmakidari S, Bhattacharya P and Chaturvedi S. Carotid artery stenosis: medical therapy, surgery, and stenting. *Current neurology and neuroscience reports* 2017; 17: 77.
38. Ahmadi R, Schillinger M, Lang W, Mlekusch W, Sabeti S and Minar E. Carotid artery stenting in older patients: is age a risk factor for poor outcome? *Journal of Endovascular Therapy* 2002; 9: 559-65.