

The Role of Carotid Doppler Ultrasound in Dementia Diagnosis and Management

Salihović Hajdarević D¹, Pavlović A^{2*}, Smajlović Dž¹, Jovanović Z² and Šternić N²

¹Department of Neurology, University Clinical Centre Tuzla, Bosnia and Herzegovina

²Department of Neurology, Clinical Centre of Serbia, Republic of Serbia

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***Corresponding author:** Aleksandra M Pavlović, Faculty of Medicine, University of Belgrade, Neurology Clinic, Clinical Center of Serbia, Dr Subotića 6, 11000 Belgrade, Serbia, Tel: + 381 11 306 42 19; Fax: + 381 11 2684 577; Email: aleksandra3003@yahoo.com

Abstract

Carotid atherosclerosis is a major risk factor for stroke, as a result of severe stenosis or distal embolization due to an unstable plaque. Ultrasound (US) evaluation of the carotid arteries is the imaging modality of choice for the screening, diagnosis, and monitoring of atherosclerotic disease of these vessels and it is very important for patients' management. Aging and increasing life expectancy of the population led to a higher incidence of dementia and cognitive impairment. Severe carotid stenosis and increased intima media thickness are both associated with cognitive decline. Also, severe internal carotid artery stenosis is a risk factor for faster progression of Alzheimer's dementia (AD). US examination may be helpful in detecting changes in global cerebral hemodynamics in patients with dementia but cannot differentiate between vascular dementia and AD. The potential effect of carotid revascularisation in highly selected cases on the course of certain types of dementia needs to be investigated in future research.

Keywords: Carotid Disease; Extracranial Ultrasound; Dementia; Diagnosis

Abbreviations: US: Ultrasound; AD: Alzheimer's dementia; VD: Vascular Dementia; TIA: Transient Ischemic Attack; IMT: Intima-media thickness; CAS: After Carotid Angioplasty and Stenting; CEA: Carotid Endarterectomy; MRI: Magnetic Resonance Imaging

Introduction

In spite of advances in primary and secondary prevention, stroke remains the third most common cause of death, the second most common cause of dementia and the most common reason for acquired disability in adulthood, with increasing number of younger survivors [1-3]. Carotid atherosclerosis is a major risk factor for stroke, as a result of stenosis or distal embolization due to an unstable plaque [2,3]. In symptomatic patients with recent transient ischemic attack (TIA) or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, carotid revascularisation significantly reduces risk for stroke [4]. Ultrasound (US) evaluation of the carotid arteries is the imaging modality of choice for the screening, diagnosis, and monitoring of atherosclerotic disease of these vessels. Extracranial Doppler US examination provides important information about carotid artery status, level of atherosclerosis, degree of stenosis, plaque quality and early signs of atherosclerosis, as well as other pathology [5]. Besides diagnostic role, there is also emerging therapeutic role of US,

transcranial Doppler in particular, in stroke neurology [6].

Aging and increasing life expectancy of the population led to a higher incidence of dementia and cognitive impairment worldwide [7]. Dementia is a syndrome caused by heterogeneous disorders, the most common being Alzheimer's (AD) and vascular dementia (VD). There is a great body of evidence associating vascular risk factors not only to VD but also to the most prevalent type of dementia, AD [8]. Controlling for vascular risk factors at an early stage may be helpful in delaying onset and progression of cognitive impairment of different etiologies [9,10]. Having in mind high prevalence of both atherosclerosis and cognitive decline in increasing aging population, and availability and validity of carotid US examination, we aimed to review evidence of the role of the carotid US in diagnosis and management of dementia.

Pathology of Carotid Artery and Ultrasound

The most common cause of cerebral ischemia is occlusive disease of the extracranial portion of the internal carotid artery

[4]. Atherosclerosis is an inflammatory degenerative disease, manifested with generalized thickening of the arteries and reduction of vessel wall elasticity, and formation of plaques leading to progressive narrowing of the lumen; plaques are also potential source of emboli [5,11]. Main stages of atherosclerosis progression comprise formation of fatty streak, development of fibrous plaque (pathological intimal thickening, cap fibroatheroma), and complicated lesion (necrotic core, intraplaque hemorrhage, fibrocalcified plaque) [4].

Carotid US is a widely used non-invasive method applied to evaluate various stages of carotid atherosclerotic disease and is extensively used in both clinical assessments and in epidemiologic and clinical studies addressing vascular risk factors and atherosclerosis [11]. Examination with the US technology provides important data indicating presence and allowing grading of the carotid atherosclerosis. Intima-media thickness (IMT), comprising full intima and media layer diameter from the endothelial surface of the vessel up to the adventitia, is usually considered to be normal if less than 0.9 mm measured at the level of the distal common carotid artery on greyscale imaging, and is often considered an early sign of atherosclerosis [4,5,12]. Carotid plaques US classification is typically based on their echogenicity visualised on examination (uniformly echolucent, predominately echolucent, predominately echogenic, uniformly echogenic, heavy calcification) [4]. In addition, examiner may describe plaques based on presumed pathohistology, as lipid, fibrous, calcified, or one of the combinations [13]. Plaque components such as increased lipid content and intraplaque bleeding are associated with an increased risk of cerebral lesions [4]. Recent advances in US examination also enabled assessment of arterial wall stiffness. E-tracking modality is a new automatized software used for monitoring of vessel wall biomechanical parameters [14,15]. Increased stiffness or reduced vessel wall elasticity expressed with beta-index higher than 6, is another marker of early atherosclerosis [16,17].

Carotid Disease and Dementia

There is evidence that severe carotid stenosis is associated with cognitive impairment, independently of other vascular risk factors [9,18,19]. Carotid stenosis detected in population older than 65 is more frequent in men than women (75% Vs. 62%), with prevalence of stenosis $\geq 50\%$ in this population also higher in men (7% Vs. 5%) [9]. Both cerebral embolism and hypoperfusion with or without silent brain infarctions are possible underlying pathological mechanisms of cognitive changes in patients with carotid disease. In both cases, a phenomenon of loss of regional cerebral autoregulation can be recognized by means of neurosonology, with the use of transcranial Doppler US [5]. Transcranial Doppler examination can in addition detect other changes in intracranial circulation associated with carotid disease and cognitive decline, such as a decrease in blood flow velocity in large arteries of the brain,

intracranial stenosis or reduced vasomotor reactivity, main mechanism of cerebral blood flow autoregulation [9,20,21]. It is important to recognize cognitive changes in patients in whom carotid revascularisation is indicated since they may be more susceptible for perioperative complications [9].

Johnston et al. [19] evaluated a large, population-based cohort with asymptomatic carotid stenosis comprising 4,006 patients and noted progressive cognitive decline in patients with severe carotid stenosis and increased IMT over 5 years. In another population-based longitudinal study, increased carotid IMT was associated with a higher risk of developing cognitive impairment during the 10-year follow-up, and was associated with poorer performance in a test of executive function 10 years later [22]. There is also evidence of association between increased IMT and decline of cognitive function 1 year after stroke, which was not associated with the finding of the carotid stenosis [23,24]. In the Baltimore Longitudinal Study of Aging, carotid IMT predicted accelerated cognitive decline, particularly in the domain of memory, among community-dwelling individuals free of vascular and neurological disease [25].

Recent large prospective French study analysed contribution of carotid atherosclerosis to incident dementia. After a mean follow-up of 5.4 years, 421 subjects developed dementia (272 AD and 83 vascular/mixed dementia), with carotid plaques being independently related to VD occurrence with HR of 1.92. Authors concluded that carotid plaque finding may improve VD risk prediction beyond known dementia risk factors [26]. Larger extracranial carotid artery calcification was significantly associated with a higher risk of dementia in a longitudinal study by Bos et al. [27] (HR 1.37). Additional analysis correcting for the type of dementia and occurrence of stroke did not alter the results.

Carotid Disease and Vascular Dementia

In patients with cerebral small vessel disease, large artery atheroma, including carotid artery, is not associated with cognitive decline [28]. Classical cases of multiinfarct dementia, subtype of VD secondary to large territorial ischemic strokes due to severe carotid stenosis or cardioembolism, are less frequently encountered nowadays, thanks to more aggressive secondary prevention measures [29]. Impaired cerebral vasomotor reactivity, which is a marker of cerebral microvascular dysfunction, is associated with poorer cognitive functions and in particular executive dysfunction among non-demented patients with concomitant carotid large-vessel disease [30]. According to results of the Osaka Follow-up Study for Carotid Atherosclerosis, a recent Japanese study enrolling 600 patients followed up for median 8.0 years, patients with carotid stenosis and lacunar infarction were significantly more likely to be diagnosed with dementia [31]. However, further analysis comprising adjustment for age and sex did not show any effect of carotid stenosis on

incident dementia, indicating that the impact of small vessel disease on dementia could be much greater than that of large vessel pathology [31,32].

Interestingly, a small study analysing sedentary and endurance-trained middle-aged adults showed that a lower carotid artery stiffness in endurance-trained adults was associated with better neuropsychological outcome and greater occipitoparietal perfusion [33]. This indicates that habitual aerobic exercise is an effective lifestyle strategy to reduce central arterial stiffness and is related to lower risk of cognitive impairment.

Carotid Disease and Degenerative Dementia

Cardinal vascular risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, and smoking, are not exclusively risk factors for VD, but also for AD [8,34,35,36]. Cerebral blood flow is reduced in patients developing MCI and AD [37], with AD patients having 20% lower cerebral flow compared to non-demented age-matched controls, confirming an association between brain hypoperfusion and AD [38]. In one prospective study on 296 patients with AD and 237 patients with vascular cognitive decline, no statistically significant differences were obtained between these two groups regarding the degree of carotid artery stenosis and carotid IMT [34]. However, AD patients more frequently had carotid artery stenosis >50% ($p=0.007$) with reported increased frequency of carotid plaques ($p<0.001$) compared to vascular group [34]. Silvestrini et al. [39] followed up for 12 months 411 AD patients, and found that more severe internal carotid artery stenosis was a risk factor for faster progression of AD. Impaired vasomotor reactivity assessed with breath-holding test also identified patients at a higher risk of rapid cognitive decline, warranting investigation of the potential benefit of carotid revascularization procedures in these patients [39]. Findings from Baltimore Longitudinal Study of Aging comprising longitudinal follow-up on cognitive decline in 364 individuals older than 60, indicate that adjusted proportional hazards models revealed >2.5-fold increased risk of dementia and AD among individuals in the upper quintile of carotid IMT, and approximately 2.0-fold increased risk of dementia among individuals with bilateral plaque [40].

Several studies aimed to analyze usefulness of extracranial ultrasound in differentiation between VD and AD. A German study [7] showed that transcranial and extracranial ultrasound are not useful in distinguishing VD and AD. However, their results add insight into the pathophysiology of dementia, arguing in favour of a common 'vascular' pathway in both conditions [7]. Morovic et al. [41] also did not find any significant difference between AD and VD patients with the use of non-invasive neurosonological methods, except for tendency of greater common carotid artery diameter and arterial stiffness in VD cases. According to Schreiber et al. [42], reduced cerebral blood flow and prolonged global cerebral circulation in both -VD and AD patients as well as

small vessel diseases patients were relevant predictors of both types of dementia. Authors concluded that US examination may be helpful in detecting changes in global cerebral hemodynamics in patients with dementia but cannot differentiate between VA and AD.

Effect of Carotid Revascularization on Cognitive Status

It has been suggested that carotid atherosclerotic disease is independently associated with cognitive dysfunction, questioning whether carotid atherosclerosis is truly silent in subclinical stages [21]. An improvement in cognitive function following revascularization may be expected since reduced embolism and improved cerebral hemodynamics are achieved. However, there are no strong data indicating a cognitive change after carotid angioplasty and stenting (CAS) or carotid endarterectomy (CEA) in patients who do not experience stroke complications, and there is no evidence to support the performance of prophylactic revascularization procedures with the aim of preventing a cognitive decline in otherwise asymptomatic patients [43].

Barrachini et al. [44] reported that only elderly symptomatic patients with severe carotid lesions had a significant improvement in cognitive performance scores after CEA, although the benefit was considered overall clinically not significant. The authors concluded that CEA does not diminish cognitive functions, but might provide some protection against cognitive decline in the elderly. However, cognitive status assessment in this study was not detailed but performed with screening tests such as Mini Mental State Examination and Montreal Cognitive Assessment. In a smaller study by Gremigni et al. [45], cognitive function measured post-CEA in asymptomatic patients using a brief standardized test improved significantly at 3 months after CEA in both patients with and without dementia.

In the study Sun et al. [46] CAS performed in 105 patients with leukoaraiosis and significant carotid stenosis (>70%) led to reduction of Clinical Dementia Rating scale scores. In a small study revascularization of severe both symptomatic and asymptomatic carotid stenosis with a carotid stent and neuroprotection left cognitive function unchanged in short-term follow-up, but in many instances cognitive function improved during one-year follow-up [47]. In spite of some positive reports, there are studies evidencing that periprocedural embolic events during carotid revascularisation can have deleterious effects on cognitive functions [21]. Zhou reported this finding with magnetic resonance imaging (MRI) evidence of distal embolization, while in the substudy of the International Carotid Stenting Study, a nonsignificant decline in cognition following CAS was seen and correlated with a twice more evident embolic events on post-procedure MRI [48,49].

A recent systematic review suggested that no obvious cognitive differences between CAS and CEA can be observed

after either intervention. Both improvement and deterioration in cognitive functioning can be observed following CAS or CEA [50]. Large-scale and methodologically high-level studies comparing CEA and CAS on cognitive outcome remain warranted, since studies published so far differed greatly in methodology, including patient heterogeneity, differences in implementation and type of control groups, psychometric tests used, statistical analyses, or timing of the assessments.

These findings led to conclusion that cognitive evaluation should be an important part of initial carotid disease evaluation. Preferably, repeat cognitive assessment should be performed beyond 3 months to show lasting rather than transient post-procedure effects. The increasing use of transcranial Doppler, MRI and other methodology to determine cerebral flow in patients evaluated for recanalization intervention should provide more information on vulnerable cohort of patients who would potentially benefit from revascularisation, especially in asymptomatic cases [21].

Conclusion

Association between atherosclerosis detected with the use of carotid Color Doppler US examination and cognitive decline of various etiologies, appears to be frequent and important for patients' management. There is a possibility that early carotid revascularisation in highly selected cases might delay or prevent onset or progression of dementia, although further research is urgently needed.

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