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Original research article

Neuropsychological tests and prediction of dementia in association with the degree of carotid stenosis

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Abstract
This study constitutes a cross sectional analysis of the association between cognitive impairment defined by neuropsychological tests and carotid stenosis. The main objective was to compare the results of the Mini-Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination-Revised (ACE-R) with regard to the degree of carotid stenosis. The sample comprised 744 patients who underwent a carotid duplex ultrasound and cognitive function testing (by ACE-R and MMSE). A multivariable analysis of potential confounding factors was completed. The significance of the different number of positive (MMSE ≤ 27, ACE-R ≤ 88) and negative (MMSE ≥ 28, ACE-R ≥ 89) results of the neuropsychological tests was analysed with regard to the degree of carotid stenosis (50–99%). Neuropsychological test results were also compared between carotid stenosis of 50–69%, 70–89%, and 90–99%. For both the MMSE and ACE-R, a difference was observed between positive and negative test results when higher degrees of stenosis were present. However, for the ACE-R only, more severe stenosis (80–89%, 90–99%) was predominantly associated with positive test results (p-value < 0.017). The same dependence for ACE-R (although not statistically significant) was observed in the group of patients without an ischemic stroke (confounding factor). In the case of the MMSE and more severe stenosis, negative results predominated, regardless of the confounding factor. There were no statistically significant differences in test results between carotid stenosis of 50–69%, 70–89%, and 90–99%. The results suggest that for assessing the early risk of cognitive impairment in patients with carotid atherosclerosis, the ACE-R appears more suitable than the MMSE.

Keywords: Atherosclerosis; Carotid stenosis; Cognitive impairment; Neuropsychological test

Highlights:
- MMSE and ACE-R positive and negative results differed in higher degrees of stenosis.
- As carotid stenosis increases, the number of patients with low ACE-R scores increases.
- In case of more severe stenosis, normal (physiological) MMSE results predominated.
- The ACE-R appears more suitable for use in patients with carotid atherosclerosis.

Abbreviations:
ACE-R – Addenbrooke's Cognitive Examination-Revised; MMSE – Mini-Mental State Examination; MoCA – Montreal Cognitive Assessment; MCI – mild cognitive impairment

Introduction

Arterial atherosclerosis is thought to greatly contribute to the development of dementia, in particular the two major subtypes, Alzheimer's and vascular dementia (Iadecola, 2010). Despite the well-known association between atherosclerosis risk factors and age-related cognitive decline, the underlying pathophysiological processes remain elusive. It is currently hypothesized that neurodegenerative and vascular lesions coexist, playing a synergistic role in the development of cognitive disorders and dementia. The association may be mediated by cerebrovascular disease such as stroke and small vessel disease (lacunar infarcts), or may result from cerebral hypoperfusion (Harlé and Plichart, 2015; Iadecola, 2010). Moreover, the carotid artery is ideally placed for ultrasound examination and assessment of atherosclerosis, potentially enabling early and intensified risk factor management to preserve cognitive

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function or delay further decline (Ihle-Hansen et al., 2021). According to several studies, cognitive function is strongly related to the degree of carotid stenosis (Ihle-Hansen et al., 2021; Lal et al., 2017; Martinić-Popović et al., 2009; Wang et al., 2016).

According to the World Alzheimer Report 2019, more than 50 million people worldwide live with dementia (Alzheimer's Disease International, 2019). This number nearly doubles every 20 years and is expected to reach 82 million by 2030 and 152 million by 2050. These new estimates are approximately 10–13% higher than those published in the World Alzheimer Report 2016 (Prince et al., 2016). Moreover, Alzheimer's Disease International claims that most people currently living with dementia are not formally diagnosed. In high-income countries, only 20–50% of dementia cases are recognized and documented by primary care. The percentage is even smaller in middle- and low-income countries (Prince et al., 2011). In the Czech Republic, the 2016 estimate was 155,900 people with dementia; the actual number is unknown (Mátl et al., 2016).

Given the diversity of clinical presentation and complex neuropathology of dementia, its classification remains controversial. The US National Plan to Address Alzheimer's Disease has proposed that Alzheimer's disease-related dementias include the following entities: Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, and mixed dementias (Raz et al., 2016). Cognitive impairment may not be recognized until it progresses to moderate or severe stages (Lin et al., 2013; Tsoi et al., 2015). In that respect, neuropsychological tests (also known as screening tests, cognitive ability tests, or cognitive tests) are rapid and useful tools for assessing patients' cognitive status (Ashford et al., 2006). The test most commonly used for screening dementia is the Mini-Mental State Examination (MMSE). However, many other neuropsychological tests have comparable diagnostic yield (Tsoi et al., 2015). According to several studies, Addenbrooke's Cognitive Examination-Revised test (ACE-R) is the best alternative neuropsychological test for dementia, and the Montreal Cognitive Assessment (MoCA) for screening mild cognitive impairment (MCI) (Tsoi et al., 2015).

The main objective of the study was to compare results of MMSE and ACE-R with regard to the degree of carotid stenosis. The study constitutes a cross sectional analysis of the association between cognitive impairment defined by neuropsychological tests and the degree of carotid stenosis. It was conducted as part of a Czech Health Research Council project entitled "Possible influence of atherosclerosis on dementia development", the main objective of which is to confirm the hypothesis that atherosclerosis considerably influences cognitive decline and significantly increases the risk of dementia in various ways.

Materials and methods

Sample

The analysis comprised ANTIQUE (Atherosclerotic Plaque Characteristics Associated with a Progression Rate of the Plaque and a Risk of Stroke in Patients with the Carotid Bifurcation Plaque Study; ClinicalTrials.gov Identifier: NCT02360137). The inclusion criteria were (1) age 30–90 years; (2) ultrasonographically detected carotid bifurcation stenosis of 50–99%, as classified by the NASCET criteria (North American Symptomatic Carotid Endarterectomy Trial, et al., 1991; von Reutern et al., 2012); and (3) written informed consent. The exclusion criterion was impairment not allowing cognitive testing (e.g., severe visual or hearing impairment). Patient examination and data collection took place between the years 2015 and 2020. First, all patients underwent an ultrasound examination with an evaluation of the degree of stenosis (see section Ultrasound examination), and only then cognitive tests (see section Cognitive testing). For the purposes of this work, patients were divided according to the results of neuropsychological tests into a group of cases and controls (see section Cognitive testing).

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Faculty of Health Sciences, Palacký University Olomouc (protocol code UPOL-83451/1040-2018, date of approval 6 June 2018; and protocol code UPOL-90360/1030-2019, date of approval 12 June 2019).

Clinical examination

On their enrolment in the study, all patients underwent neurological and physical examinations. Their blood pressure was taken (a single measurement at rest following ultrasound examination) and demographic and clinical data were recorded such as age, sex, medical history (arterial hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, atrial fibrillation, myocardial infarction or other heart diseases, stroke including its type, surgery or stenting including that of carotid, coronary, or leg arteries), smoking, alcohol consumption, and medicines.

Ultrasound examination

All participants underwent a standard ultrasound scan using the Mindray DC8 duplex ultrasound system (Mindray, Shenzhen, China) with a 3–12 MHz linear transducer (L12-3E). The neck arteries (both carotid and vertebral) were examined and flow curves were obtained for all intracranial arteries visible. For all plaques causing carotid bifurcation stenosis of 50–99%, 10s sequences were recorded in the longitudinal and cross-sectional planes to assess plaque characteristics including the thickness, residual lumen, flow curves showing the peak, median and end-diastolic velocity. The parameters were used to determine the severity of stenosis expressed as a percentage, according to previously published criteria (Stegehuis et al., 2018; von Reutern et al., 2012). The ultrasound was performed by nationally certified neurologists for performing neurosonological examinations. Scales were also performed by neurologists.

Cognitive testing

In all patients, cognitive functioning was assessed with the MMSE and ACE-R (a revised Czech version). The tests were performed under previously defined standard conditions (Molloy and Standish, 1997). The raters had long-term experience and were trained for administration of the tests. The MMSE results were assessed using a cut-off of ≤ 27 points for early detection of cognitive impairment. These results were considered positive for cognitive impairment screening. Scores higher than 27 points were considered negative. In case of the ACE-R, the cut-off for dementia, or Alzheimer's disease, early detection was ≤ 88 points (Mioshi et al., 2006). Scores above 88 points were deemed negative. Patients with MMSE scores ≥28 points and ACE-R scores ≥ 89 points had negative neuropsychological test results (*i.e.*, normal findings) and thus comprised a control group (without cognitive impairment). Both test cut off points were tested for the Czech population in previous studies (Bartos and Raisova, 2016; Bartos et al., 2011; Hummelová-Fanfrdlová et al., 2009).

Statistical analysis

The normality of data distribution was evaluated with the Shapiro–Wilk test. Demographic data are presented as mean and standard deviation (SD), median and interquartile range, or number and percentage. A multivariable analysis of potential confounding factors was completed for quantitative variables by correlation and regression analysis, and for dichotomous variables by *t*-test, or nonparametric Mann–Whitney *U* test. Further, frequency tables were used to group individual data concerning stenosis percentages and neuropsychological test results. Data on stenosis severity were divided into groups by 10 percentage points (50–59%, 60–69%, 70–79%, 80–89%, 90–99%). Neuro-psychological test results were classified according to the following diagnostic criteria for the presence of cognitive impairment: MMSE ≤ 27 (presence of dementia MMSE ≤ 24), ACE-R ≤ 88. The significance of differences between positive (MMSE ≤ 27, ACE-R ≤ 88) and negative (MMSE ≥ 28, ACE-R ≥ 89) test results with regard to stenosis groups was evaluated with a *z*-test. Statistical comparison of neuropsychological test (MMSE, ACE-R) results among patients grouped by the degree of stenosis (50–69%, 70–89%, 90–99%) was made with a two-sample *z*-test. The statistical tests were performed at a significance level of 5%. The analyses were achieved using Statistica 13.4 (TIBCO Software Inc, Palo Alto, USA).

Results

The sample comprised 744 patients. There was a preponderance of males (70%). The mean age of participants was 68.2 years (± SD 7.6). All patients were diagnosed with carotid stenosis of 50–99%. The mean MMSE and ACE-R scores were 27.5 (± SD 3.0) and 84.4 (± SD 11.0) points, respectively. Patients were divided into a group of cases and controls separately according to the results of ACE-R and MMSE. The baseline characteristics of the study groups are listed in Table 1.

Table 1. Baseline characteristics of the study groups divided according to the cognitive tests results

	Study groups according to the cognitive test results			
	ACE-R		MMSE	
Characteristics	Cases (*n* = 427) Mean ± SD or *N* (%)	Controls (*n* = 317) Mean ± SD or *N* (%)	Cases (*n* = 254) Mean ± SD or *N* (%)	Controls (*n* = 490) Mean ± SD or *N* (%)
Age (years)	69.4 ± 7.5	66.6 ± 7.5	69.9 ± 7.6	67.3 ± 7.5
Gender				
Female	140 (33)	83 (26)	82 (32)	141 (29)
Male	287 (67)	234 (74)	172 (68)	349 (71)
Ischemic event				
In sum	263 (62)	168 (53)	165 (65)	266 (54)
Ischemic stroke	164 (38)	90 (28)	106 (42)	148 (30)
TIA	89 (21)	54 (17)	51 (20)	92 (19)
Amaurosis fugax	20 (5)	26 (8)	12 (5)	34 (7)
Retinal infarction	4 (1)	8 (3)	5 (2)	7 (1)
Hypertension	371 (87)	279 (88)	219 (86)	432 (88)
Diabetes	162 (38)	102 (32)	92 (36)	172 (35)
Hyperlipidemia	352 (82)	262 (83)	197 (78)	417 (85)
Coronary heart disease	134 (31)	100 (32)	81 (32)	153 (31)
Myocardial infarction	66 (15)	42 (13)	34 (13)	74 (15)
Atrial fibrillation	35 (8)	19 (6)	23 (9)	31 (6)
Smoking				
Smokers	158 (37)	134 (42)	94 (37)	198 (40)
Non-smokers	223 (52)	148 (47)	126 (50)	245 (50)
Ex-smokers	38 (9)	34 (11)	84 (33)	44 (9)
Alcohol consumption				
Consumers	183 (43)	157 (50)	115 (45)	225 (46)
Abstainers	225 (53)	153 (48)	128 (50)	250 (51)
Carotid stenosis side				
Left	200 (47)	129 (41)	120 (47)	209 (43)
Right	210 (49)	180 (57)	125 (49)	265 (54)

Note: SD – standard deviation.

Fig. 1 shows the relative frequencies of subjects with regard to neuropsychological test results and degrees of carotid stenosis. It can be seen that with increasing stenosis severity, the difference (in percent) increases between patients with positive and negative ACE-R results (cases and controls). This is because rising stenosis percentages are associated with higher proportions of positive ACE-R results. For the MMSE, no significant relationship with stenosis severity was observed, with negative MMSE results predominating in all stenosis groups.

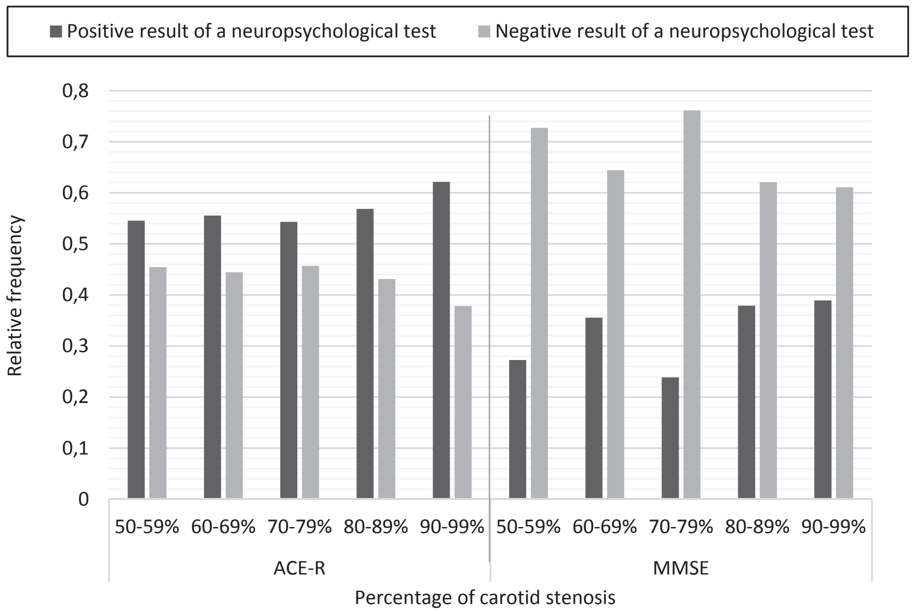

Fig. 1. Relative frequencies of subjects with regard to neuropsychological test results and percentages of carotid stenosis

The results of the multivariable analysis of potential confounding factors (Iulita et al., 2018) in the studied sample are shown in Table 2. Randomized age is a statistically significant confounding factor for positive results of neuropsychological tests used (presence of cognitive impairment). For both stenosis and cognitive impairment, ischemic stroke is an especially statistically significant confounding factor ($p < 0.003$). Based on this finding, follow-up analyses were performed separately in the group of all patients and in the group of patients without ischemic stroke. Because neuropsychological tests are used both for screening of the general population – regardless of "comorbidities" – and also in the diagnosis in the case of a specific population, analyses of both groups were performed.

Table 2. A multivariable analysis of potential confounding factors

Variable	Stenosis	ACE-R positive	MMSE positive
	p-value or correlation coefficient (*r*)		
Age-randomized	$r = 0.0599$	$r = -0.192$*	$r = -0.115$*
Ischemic stroke	0.0034*	<0.001*	0.003*
TIA	NS	NS	NS
Amaurosis fugax	NS	0.028*	NS
Retinal infarction	NS	NS	NS
Hypertension	NS	NS	NS
Diabetes mellitus	NS	NS	NS
Hyperlipidemia	NS	NS	NS
Coronary heart disease	NS	NS	0.006*
Ischemic stroke	0.0034*	<0.001*	0.003*

* Statistically significant at $p < 0.05$; NS not statistically significant.

Tables 3 and 4 list absolute and relative numbers of subjects by neuropsychological test (MMSE, ACE-R) results for the group of all patients and patients without ischemic stroke, with statistical significance of the difference between positive and negative test results, for each stenosis severity group. The results suggest that in the case of the MMSE, statistically significant differences between positive and negative results were observed in all patients with stenosis of 70–79%, 80–89%, and 90–99%. Most of these patients, however, had negative MMSE results, that is, this test failed to detect cognitive impairment in most patients with high stenosis percentages. Similarly, there were statistically significant differences between positive and negative ACE-R test results in patients with severe stenosis (namely 80–89% and 90–99%). However, positive test results predominated, *i.e.*, the proportion of patients detected with cognitive impairment using the test increased with carotid stenosis severity.

Table 3. Absolute and relative numbers of subjects by MMSE results, with statistical significance of the difference between positive and negative test results, for each stenosis severity group

Stenosis	MMSE positive		MMSE negative	Total	*p*-value
	0–24 pts.[a]	25–27 pts.[b]	28–30 pts.		
	N (%)	*N* (%)	*N* (%)	*N* (%)	
Group of all patients (*n* = 744)					
50–59%	3 (27.27)	0 (0.00)	8 (72.73)	11 (100)	0.170
60–69%	4 (8.89)	12 (26.67)	29 (64.44)	45 (100)	0.063
70–79%	21 (10.66)	26 (13.20)	150 (76.14)	197 (100)	<0.001***
80–89%	33 (10.78)	83 (27.12)	190 (62.09)	306 (100)	<0.001***
90–99%	32 (17.30)	40 (21.62)	113 (61.08)	185 (100)	0.003**
Total	93 (12.50)	161 (21.64)	490 (65.86)	744 (100)	<0.001***
Group of patients without ischemic stroke (*n* = 490)					
50–59%	2 (50.00)	0 (0.00)	2 (50.00)	4 (100)	1.000
60–69%	2 (7.14)	6 (21.43)	20 (71.43)	28 (100)	0.037*
70–79%	8 (6.90)	19 (16.38)	89 (76.72)	116 (100)	<0.001***
80–89%	15 (7.08)	57 (26.89)	140 (66.04)	212 (100)	<0.001***
90–99%	17 (13.08)	22 (16.92)	91 (70.00)	130 (100)	<0.001***
Total	44 (8.98)	104 (21.22)	342 (69.80)	490 (100)	<0.001***

[a] MMSE criterion for dementia; [b] MMSE criterion for MCI; *–*** level of statistical significance.

Table 4. Absolute and relative numbers of subjects by ACE-R results, with statistical significance of the difference between positive and negative test results, for each stenosis severity group

Stenosis	ACE-R positive	ACE-R negative	Total	*p*-value
	0–88 pts.	89–100 pts.		
	N (%)	*N* (%)	*N* (%)	
Group of all patients (*n* = 744)				
50–59%	6 (54.55)	5 (45.45)	11 (100)	0.764
60–69%	25 (55.56)	20 (44.44)	45 (100)	0.459
70–79%	107 (54.31)	90 (45.69)	197 (100)	0.228
80–89%	174 (56.86)	132 (43.14)	306 (100)	0.017*
90–99%	115 (62.16)	70 (37.84)	185 (100)	0.001***
Total	427 (57.39)	317 (42.61)	744 (100)	<0.001***
Group of patients without ischemic stroke (*n* = 490)				
50–59%	2 (50.00)	2 (50.00)	4 (100)	1.000
60–69%	11 (39.29)	17 (60.71)	28 (100)	0.268
70–79%	64 (55.17)	52 (44.83)	116 (100)	0.268
80–89%	113 (53.30)	99 (46.70)	212 (100)	0.338
90–99%	73 (56.15)	57 (43.85)	130 (100)	0.164
Total	263 (53.67)	227 (46.33)	490 (100)	0.088

* – *** level of statistical significance.

In the case of patients without ischemic stroke, the situation was similar for MMSE. Statistically significant differences between positive and negative MMSE results were observed in patients without ischemic stroke with stenosis of 70–79%, 80–89%, 90–99%, and in addition with stenosis of 60–69%. In all cases, negative MMSE results prevailed. The opposite situation was observed for ACE-R results in patients without ischemic stroke. No statistically significant difference was found between positive and negative ACE-R results in all groups of carotid stenosis, but in higher stenosis positive ACE-R results prevailed (Table 4).

Table 5 shows the characteristics of MMSE and ACE-R results, providing a statistical comparison of the results among patients grouped by the severity of stenosis (50–69%, 70–89% and 90–99%). This comparison failed to show statistically significant differences among both patient groups (all patients and patients without ischemic stroke) and thus various degrees of stenosis. However, as seen from the mean scores of neuropsychological tests, the mean MMSE score is nearly identical to the test cut-off values between positive and negative results. By contrast, the mean ACE-R score is clearly below the cut-off for positive test results, except in patients without ischemic stroke and stenosis 50–69%, where the mean ACE-R score is nearly identical to the cut off value (88 points).

Table 5. Characteristics of neuropsychological test results and statistical comparison among patients grouped by the degree of stenosis

Degree of stenosis	Characteristics of neuropsychological test results						*p*-value	
	Min	Mean	Med	Max	SD	Variance	Sten. 70–89%	Sten. 90–99%
All patients (*n* = 744)								
MMSE								
Stenosis 50–69% (*n* = 56)	17.0	27.5	28.0	30.0	2.7	7.3	0.799	0.444
Stenosis 70–89% (*n* = 503)	10.0	27.6	29.0	30.0	2.9	8.6	–	0.073
Stenosis 90–99% (*n* = 185)	12.0	27.1	28.0	30.0	3.2	10.1	–	–
ACE-R								
Stenosis 50–69% (*n* = 56)	62.0	85.4	87.5	99.0	9.9	97.4	0.685	0.180
Stenosis 70–89% (*n* = 503)	36.0	84.8	87.0	100.0	10.5	111.1	–	0.128
Stenosis 90–99% (*n* = 185)	6.0	83.2	86.0	99.0	12.3	151.3	–	–
MMSE								
Stenosis 50–69% (*n* = 56)	17.0	27.6	29.0	30.0	3.0	8.8	0.545	0.799
Stenosis 70–89% (*n* = 503)	16.0	27.9	29.0	30.0	2.3	5.2	–	0.408
Stenosis 90–99% (*n* = 185)	18.0	27.7	28.0	30.0	2.5	6.1	–	–
ACE-R								
Stenosis 50–69% (*n* = 32)	62.0	88.3	91.0	99.0	8.6	74.3	0.132	0.108
Stenosis 70–89% (*n* = 328)	36.0	85.7	88.0	100.0	9.4	87.3	–	0.750
Stenosis 90–99% (*n* = 130)	6.0	85.4	87.0	99.0	11.1	123.7	–	–

Note: SD – standard deviation.

Discussion

According to epidemiological studies, atherosclerosis (in particular carotid atherosclerosis) may predict the development of dementia (Harlé and Plichart, 2015). However, the pathophysiological pathways are still not completely clear. Multiple risk factors have been found to be associated with atherosclerosis, for example obesity, cigarette smoking, arterial hypertension, diabetes mellitus or hypercholesterolemia (Hajar, 2017; Janoutová et al., 2020). To a great extent these risk factors are modifiable. Therefore, they may be addressed by prevention to avoid not only atherosclerosis but also dementia. With increasing life expectancy, the incidence rates of both atherosclerosis and dementia are expected to rise. It is therefore essential to search for new optimal ways of their modification in the population (Janoutová et al., 2020; Zatloukalová et al., 2020). From that perspective, an effective approach may be the use of neuropsychological tests. These are used both to identify patients with early cognitive impairment (e.g., MCI or early-stage Alzheimer's disease) and to stage cognitive impairment, support the diagnosis, determine the initiation of therapy, and monitor its effect (Janoutová et al., 2018). Given the reported association between carotid atherosclerosis and cognitive impairment, the question arises as to how the association is reflected by these neuropsychological tests. Studies have generally shown that patients with carotid stenosis have statistically significantly worse neuropsychological test results than controls (Martinić-Popović et al., 2012). However, there is a dearth of studies comparing results of various neuropsychological tests in association with the degree of carotid stenosis. The presented study compares MMSE and ACE-R results with regard to the degree of carotid stenosis.

MMSE is the most commonly test used for screening dementia. According to a systematic review of Tsoi et al. (2015), the ACE-R is one of the best alternatives with comparable diagnostic effects. The combined sensitivity and specificity for detection of dementia were 0.81 and 0.89, respectively, for the MMSE, and 0.92 and 0.89, respectively, for the ACE-R (Tsoi et al., 2015). Thus, the latter neuropsychological test showed higher sensitivity and comparable specificity. For screening MCI, the best possible alternative was found to be the MoCA, with 0.89 sensitivity and 0.75 specificity (Tsoi et al., 2015).

In a study by Mathiesen et al. (2004), assessing the relationship between asymptomatic carotid stenosis and neuropsychological tests, subjects with carotid stenosis had significantly lower performance in tests of attention, memory, psychomotor speed, and motor functioning. However, cognitive problems of patients with advanced carotid stenosis are usually mild and not severe enough to affect their everyday activities. That is why these problems are not recognized by patients, their families, or close friends (Sztriha et al., 2009). Since such cognitive changes do not meet the criteria for diagnosing dementia, they are defined as MCI (Martinić-Popović et al., 2012). Studies report that in these cases, the MMSE has low sensitivity and is therefore not recommended for screening MCI (Nasreddine et al., 2005; Tombaugh and McIntyre, 1992). Patients with MCI (e.g., those with carotid artery disease) find tasks contained in the MMSE rather simple (Martinić-Popović et al., 2012).

This is also consistent with the present study, which failed to show a relationship between MMSE results and the degree of carotid stenosis, despite the use of a higher recommended cut-off for detecting MCI (MMSE ≤ 27) compared to the cut-off recommended for detecting dementia (MMSE ≤ 24) (Bartos and Raisova, 2016; Lin et al., 2013). In the entire sample, negative MMSE results predominated (MMSE ≥ 28, in patients with higher stenosis percentages *p*-value < 0.003, see Fig. 1, Table 3). The opposite was true for the ACE-R (Fig. 1, Table 4). There was a statistically significant difference between negative and positive test results in patients with more severe carotid stenosis (namely 80–89% and 90–99%). Unlike the MMSE, positive test results were more prevalent with the ACE-R (≤88, *p*-value < 0.017), that is, the proportion of patients detected with dementia increased with carotid stenosis severity.

By multivariable analysis of our sample, it was found that ischemic stroke is a statistically significant confounding factor for both stenosis and dementia (assessed as a positive result by ACE-R and MMSE). Based on this finding, a separate statistical analysis of the group of patients without an ischemic stroke was performed. In the case of MMSE, the same as in the group of all patients, negative MMSE results (≥28) predominated with higher stenosis percentages ($p < 0.037$, Table 2). The difference occurred in the case of ACE-R, where compared to the group of all patients, no statistically significant difference was found between positive and negative results in the group of patients without ischemic stroke. As in the case of the group of all patients, the positive results of ACE-R still prevailed, especially at higher degrees of stenosis. Reduction of the subject number in the group of patients without ischemic stroke could be the cause of statistical insignificance. There is a lack of knowledge of the isolated impact of neurologically asymptomatic carotid stenosis (without stroke) on cognitive function. This is because of concomitant vascular risk factors, which can confound vascular cognitive impairment, as for example Lal et al. (2017) state in their work. According to these authors, such an impairment can be mediated by micro-embolic ischemic brain injury from an unstable carotid plaque and cerebrovascular hemodynamic impairment (Lal et al., 2017). A circumscribed ischemia with local flow decrease may result in different cognitive abnormalities to those with diffuse hypoperfusion caused by carotid stenosis. According to the study of Scherr et al. (2012), carotid artery stenosis in stroke-free patients negatively correlated with measures of verbal fluency, constructional praxis, verbal short-term memory, semantic processing, speed of cognitive processing, and divided attention.

The ACE-R is a revised version of the original ACE (Mathuranath et al., 2000). The test was developed to overcome some shortcomings of the MMSE. Compared to the MMSE, the ACE-R (ACE) contains more memory and visuospatial ability items, as well as tests of executive function. In their meta-analysis, Larner and Mitchell (2014) revealed that the ACE-R has better diagnostic accuracy than the MMSE alone. The first Czech adaptation of the ACE-R was found to have 1.00 sensitivity for detecting Alzheimer's disease with a cut-off of 88 points and 0.96 sensitivity with a lower cut-off of 83 points (Hummelová-Fanfrdlová et al., 2009). According to several studies (Alexopoulos et al., 2010; Fang et al., 2014; Yoshida et al., 2012), the ACE-R (and its various language versions) is more sensitive and accurate in detecting MCI or mild Alzheimer's disease than the MMSE. In that respect, the ACE-R seems to be more suitable for the identification of patients with MCI including, for example, those with carotid artery disease, which is consistent with results in a group of all patients of the presented study.

Due to potential licensing problems with the ACE-R, another version was developed under the name ACE-III (Habib and Scott, 2019). There are only minimal differences between the two versions. For example, a study by Hsieh et al. (2013) analyzing both tests concluded that their correlation is almost perfect ($r = 0.99$). Subsequently, an abridged version of the ACE-III was made, referred to as Mini-ACE (M-ACE). According to a systematic review (Beishon et al., 2019), assessing the diagnostic accuracy of these two latest versions (ACE-III and M-ACE) for the detection of dementia, its subtypes and MCI, there is insufficient information to assess their accuracy and further research is needed.

The present study also statistically compared MMSE and ACE-R results among groups of patients with various degrees of stenosis. Patients were divided into groups with carotid stenosis of 50–69%, 70–89%, and 90–99%. This division was based on the fact that stenosis of 50–70% is associated with no hemodynamic effects (no reduction in flow rate beyond the stenosis), unlike stenosis of more than 70% or 75%. Stenosis of more than 90% or 95% (pre-occlusive stenosis) results in minimal flow rate per minute and markedly reduced flow velocity (Školoudík et al., 2003). The comparison failed to show statistically significant differences in neuropsychological test results among the patient groups and thus various degrees of stenosis. However, comparison of the mean total scores of neuropsychological tests shows that the mean MMSE score (27.1–27.6 ± SD 2.7–3.2) is nearly identical to the cut-off between positive and negative results. By contrast, the mean ACE-R score (83.2–85.4 ± SD 9.9–12.3) is clearly below the cut-off for positive test results.

Conclusions

The published studies generally show statistically significantly worse neuropsychological test results in patients with carotid stenosis than in control groups. However, there is a dearth of studies comparing the results of various neuropsychological tests in association with the degree of carotid stenosis. In the presented study, only ACE-R corresponded with carotid stenosis severity, *i.e.*, a statistically significantly higher proportion of patients with cognitive impairment (ACE-R ≤ 88) was observed depending on the carotid stenosis severity. The same dependence for ACE-R (although not statistically significant) was observed in a group of patients without an ischemic stroke (as an identified confounding factor). In all groups of stenosis severity, normal (physiological) MMSE results predominated, *i.e.*, cognitive changes were not detected, regardless of the ischemic stroke as a confounding factor.

Because cognitive problems of patients with advanced carotid stenosis are usually mild and not severe enough to be diagnosed as dementia, they are defined as MCI. Studies report that in these cases, the MMSE has low sensitivity and is therefore not recommended for screening MCI. Thus, the study results suggest that for assessing the early risk of cognitive impairment in patients with carotid atherosclerosis, the ACE-R appears more suitable than the MMSE. Further research is needed to confirm causal dependence.

Ethical aspects and conflict of interests

The authors have no conflict of interests to declare.

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References

Alexopoulos P, Ebert A, Richter-Schmidinger T, Schöll E, Natale B, Aguilar CA, et al. (2010). Validation of the German Revised Addenbrooke's Cognitive Examination for Detecting Mild Cognitive Impairment, Mild Dementia in Alzheimer's Disease and Frontotemporal Lobar Degeneration. Dement Geriatr Cogn Disord 29: 448–456. DOI: 10.1159/000312685.

Alzheimer's Disease International (2019). World Alzheimer Report 2019. Attitudes to Dementia. [online] [cit. 2022-01-22]. Available from: https://www.alzint.org/u/WorldAlzheimerReport2019.pdf

Ashford JW, Borson S, O'Hara R, Dash P, Frank L, Robert P, et al. (2006). Should Older Adults Be Screened for Dementia? It is important to screen for evidence of dementia! Alzheimers Dement 3(2): 75–80. DOI: 10.1016/j.jalz.2007.03.005.

Bartos A, Raisova M (2016). The Mini-Mental State Examination: Czech Norms and Cutoffs for Mild Dementia and Mild Cognitive Impairment Due to Alzheimer's Disease. Dement Geriatr Cogn Disord 42(1–2): 50–57. DOI: 10.1159/000446426.

Bartos A, Raisova M, Kopecek M (2011). The Reasons and the Process of Amendment of the Czech Addenbrooke's Cognitive Examination (ACE-CZ). Cesk Slov Neurol N 107(6): 1–5.

Beishon LC, Batterham AP, Quinn TJ, Nelson CP, Panerai RB, Robinson T, Haunton VJ (2019). Addenbrooke's Cogni-tive Examination III (ACE-III) and Mini-ACE for the Detection of Dementia and Mild Cognitive Impairment. Cochrane Database Syst Rev 12(12): CD013282. DOI: 10.1002/14651858.CD013282.pub2.

Fang R, Wang G, Huang Y, Zhuang J-P, Tang H-D, Wang Y, et al. (2014). Validation of the Chinese Version of Addenbrooke's Cognitive Examination-Revised for Screening Mild Alzheimer's Disease and Mild Cognitive Impairment. Dement Geriatr Cogn Disord 37(3–4): 223–231. DOI: 10.1159/000353541.

Habib N, Stott J (2019). Systematic Review of the Diagnostic Accuracy of the Non-English Versions of Addenbrooke's Cognitive Examination – Revised and III. Aging Ment Health 23(3): 297–304. DOI: 10.1080/13607863.2017.1411882.

Hajar R (2017). Risk Factors for Coronary Artery Disease: Historical Perspectives. Heart Views 18(3): 109–114. DOI: 10.4103/HEARTVIEWS.HEARTVIEWS_106_17.

Harlé L-M, Plichart M (2015). Carotid Atherosclerosis and Dementia. Geriatr Psychol Neuropsychiatr Vieil 13(3): 309–316. DOI: 10.1684/pnv.2015.0554.

Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR (2013). Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. Dement Geriatr Cogn Disord 36(3–4): 242–250. DOI: 10.1159/000351671.

Hummelová-Fanfrdlová Z, Rektorová I, Sheardová K, Bartoš A, Línek V, Ressner, P, et al. (2009). Czech Adaptation of Addenbrooke's Cognitive Examination. Cesk Psychol 53(4): 376–388.

Iadecola C (2010). The Overlap between Neurodegenerative and Vascular Factors in the Pathogenesis of Dementia. Acta Neuropathol 120(3): 287–296. DOI: 10.1007/s00401-010-0718-6.

Ihle-Hansen H, Ihle-Hansen H, Sandset EC, Hagberg G (2021). Subclinical Carotid Artery Atherosclerosis and Cognitive Function: A Mini-Review. Front Neurol Jul 28: 705043. DOI: 10.3389/fneur.2021.705043.

Iulita MF, Noriega de la Colina A, Girouard H (2018). Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? J Neurochem 144(5): 527–548. DOI: 10.1111/jnc.14235.

Janoutová J, Ambroz P, Kovalová M, Machaczka O, Němček K, Zatloukalová A, et al. (2018). Epidemiology of Mild Cognitive Impairment. Cesk Slov Neurol N 81(3): 284–289. DOI: 10.14735/amcsnn2018284.

Janoutová J, Kovalová M, Ambroz P, Machaczka O, Zatloukalová A, Němček K, et al. (2020). Possible Prevention of Alzheimer's Disease. Cesk Slov Neurol N 83(1): 28–32. DOI: 10.14735/amcsnn202028.

Lal BK, Dux MC, Sikdar S, Goldstein C, Khan AA, Yokemick J, Zhao L (2017). Asymptomatic carotid stenosis is associated with cognitive impairment. J Vasc Surg 66(4): 1083–1092. DOI: 10.1016/j.jvs.2017.04.038.

Larner AJ, Mitchell AJ (2014). A Meta-Analysis of the Accuracy of the Addenbrooke's Cognitive Examination (ACE) and the Addenbrooke's Cognitive Examination-Revised (ACE-R) in the Detection of Dementia. Int Psychogeriatr 26(4): 555–563. DOI: 10.1017/S1041610213002329.

Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E (2013). Screening for Cognitive Impairment in Older Adults: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med 159(9): 601–612. DOI: 10.7326/0003-4819-159-9-201311050-00730.

Martinić-Popović I, Lovrenčić-Huzjan A, Demarin V (2009). Assessment of subtle cognitive impairment in stroke-free patients with carotid disease. Acta Clin Croat 48(3): 231–240.

Martinić-Popović I, Lovrenčić-Huzjan A, Demarin V (2012). Advanced Asymptomatic Carotid Disease and Cognitive Impairment: An Understated Link? Stroke Res Treat 2012: 981416. DOI: 10.1155/2012/981416.

Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bønaa KH (2004). Reduced Neuropsychological Test Performance in Asymptomatic Carotid Stenosis: The Tromso Study. Neurology 62(5): 695–701. DOI: 10.1212/01.WNL.0000113759.80877.1F.

Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR (2000). A Brief Cognitive Test Battery to Differentiate Alzheimer's Disease and Frontotemporal Dementia. Neurology 55(11): 1613–1620. DOI: 10.1212/01.wnl.0000434309.85312.19.

Mátl O, Mátlová M, Holmerová I (2016). Zpráva o stavu demence 2016. Praha: Česká alzheimerovská společnost, o. p. s. [online] [cit. 2022-01-22]. Available from: https://www.alzheimer.cz/res/archive/004/000480.pdf?seek=1492589048

Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry 21(11): 1078–1085. DOI: 10.1002/gps.1610.

Molloy DW, Standish TI (1997). A Guide to the Standardized Mini-Mental State Examination. Int Psychogeriatr 9(Suppl. 1): 87–94. DOI: 10.1017/S1041610297004754.

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc 53(4): 695–699. DOI: 10.1111/j.1532-5415.2005.53221.x.

North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, et al. (1991). Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High-Grade Carotid Stenosis. N Engl J Med 325: 445–453. DOI: 10.1056/NEJM199108153250701.

Prince M, Bryce R, Ferri C (2011). World Alzheimer Report 2011: The Benefits of Early Diagnosis and Intervention. Alzheimer's Disease International. [online] [cit. 2022-01-22]. Available from: https://www.alzint.org/u/WorldAlzheimerReport2011.pdf

Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M (2016). World Alzheimer Report 2016: Improving Healthcare for People Living with Dementia. Alzheimer's Disease International. [online] [cit. 2022-01-22]. Available from: https://www.alzint.org/u/WorldAlzheimerReport2016.pdf

Raz L, Knoefel J, Bhaskar K (2016). The Neuropathology and Cerebrovascular Mechanisms of Dementia. J Cereb Blood Flow Metab 36(1): 172–186. DOI: 10.1038/jcbfm.2015.164.

Scherr M, Trinka E, Mc Coy M, Krenn Y, Staffen W, Kirschner M, et al. (2012). Cerebral hypoperfusion during carotid artery stenosis can lead to cognitive deficits that may be independent of white matter lesion load. Curr Neurovasc Res 9(3): 193–199. DOI: 10.2174/156720212801619009.

Školoudík D, Škoda O, Bar M, Brozman M, Václavík D (2003). Neurosonologie. Prague: Galén, 304 p.

Stegehuis VE, Wijntjens GW, Murai T, Piek JJ, van de Hoef TP (2018). Assessing the Haemodynamic Impact of Coronary Artery Stenoses: Intracoronary Flow Versus Pressure Measurements. Eur Cardiol 13(1): 46–53. DOI: 10.15420/ecr.2018:7:2.

Sztriha LK, Nemeth D, Sefcsik T, Vecsei L (2009). Carotid Stenosis and the Cognitive Function. J Neurol Sci 283(1–2): 36–40. DOI: 10.1016/j.jns.2009.02.307.

Tombaugh TN, McIntyre NJ (1992). The Mini-Mental State Examination: A Comprehensive Review. J Am Geriatr Soc 40(9): 922–935. DOI: 10.1111/j.1532-5415.1992.tb01992.x.

Tsoi KK, Chan JY, Hirai HW, Wong SY, Kwok TC (2015). Cognitive Tests to Detect Dementia: A Systematic Review and Meta-analysis. JAMA Intern Med 175(9): 1450–1458. DOI: 10.1001/jamainternmed.2015.2152.

von Reutern G-M, Goertler M-W, Bornstein NM, Del Sette M, Evans DH, Hetzel A, et al. (2012). Grading Carotid Stenosis Using

Ultrasonic Methods. Stroke 43(3): 916–921. DOI: 10.1161/STROKEAHA.111.636084.

Wang T, Mei B, Zhang J (2016). Atherosclerotic carotid stenosis and cognitive function. Clin Neurol Neurosurg 146: 64–70. DOI: 10.1016/j.clineuro.2016.03.027.

Yoshida H, Terada S, Honda H, Kishimoto Y, Takeda N, Oshima E, et al. (2012). Validation of the Revised Addenbrooke's Cognitive Examination (ACE-R) for Detecting Mild Cognitive Impairment and Dementia in a Japanese Population. Int Psychogeriatr 24(1): 28–37. DOI: 10.1017/S1041610211001190.

Zatloukalová A, Roubec M, Školoudík D, Ambroz P, Machaczka O, Janoutová J, Janout V (2020) Atherosklerosis and Dementia. Profese online 13(1): 17–21. DOI: 10.5507/pol.2020.007.