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Mild cognitive impairment in symptomatic and asymptomatic cerebrovascular disease

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Abstract

We tried to evaluate and to compare usefulness of two brief cognitive tests in early detection of cognitive decline in subjects with increased cerebrovascular (CV) risk. As CV risk factors are recognised as important in etiology of dementia, we also aimed to determine the possible associations of specific CV risk factors and cognitive results. Patients (PGs) with first-ever stroke or TIA ($N=110$) and CV symptoms-free controls (CGs) with CV risk factors present ($N=45$) matched for age, gender and education level were tested using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) on admission, at three- and six-month points. In all subjects, detailed CV risk factors profile was assessed. We observed the decrement in cognitive performance during the six-month study period in both groups, more evident if MoCA ($p<0.001$) than if MMSE was used ($p=0.022$). Six months after first stroke/TIA 83.6% PGs scored below normal range on MoCA. In PGs, positive associations for cognitive decrement and multiple CV risk factors (>2) were found ($p=0.034$ for MMSE; $p=0.002$ for MoCA). In CGs, positive associations were found for cognitive decrement and arterial hypertension with increased IMT values ($p<0.001$ for MMSE) and for multiple CV risk factors and arterial hypertension ($p=0.003$ for MoCA). The use of MoCA could aid to early recognition of cognitive deficits in persons with increased CV risk. Individuals with multiple CV risk factors seem to have increased risk of cognitive decline.

Keywords: Brain-pathology; Brain-physiopathology; Cerebrovascular disease-diagnostics; Dementia — Alzheimer's disease; Dementia — vascular dementia

1. Introduction

The term «mild cognitive impairment» (MCI) refers to a transitional stage between cognitive changes of normal aging and dementia, of both Alzheimer's (AD) and vascular type (VaD) [1]. During this stage, cognitive decline is subtle and of insufficient severity to constitute dementia, yet it is beyond for what is expected for normal aging [1]. Previous longitudinal studies showed conversion rate of patients with MCI to Alzheimer's disease of 10–30% per year [1,2] while cognitively normal elderly control subjects typically develop dementia at a rate of 1–2% annually [1]. Early diagnosis of MCI offers possibilities for potential treatment with the aim of delaying the onset or preventing dementia, either of Alzheimer's, vascular or mixed type. In assessment of MCI patients wide battery of neuropsychological testing is commonly used [3,4]. Neuropsychological testing with standardised tests, however, often presents a problem for a clinician for its complicated and time-consuming nature. Mini-Mental State Examination (MMSE) [5] is still the most widely used in assessment of patients with memory complaints, although it lacks sensitivity in detecting MCI or early stages of dementia [4,6]. Most individuals meeting clinical criteria for MCI score above 26 points on the MMSE, which is also normal range for elderly individuals. Recent study has demonstrated that combined MMSE and Clock Drawing Test (CDT) have fair sensitivity and specificity in screening for MCI [7]. Montreal Cognitive Assessment (MoCA) which was recently developed by Nasreddine et al., is easily administered and a brief screening tool with high sensitivity and specificity for MCI [8]. While MMSE is superior for more advanced stages of cognitive decline, MoCA is useful for the mild stages of cognitive impairment and for distinguishing patients with MCI from cognitively intact patients, which makes it a practical tool for

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first line physicians [8]. Previous study assessed superior sensitivity and specificity of MoCA in detection of MCI preceding early stages of AD [8]. To our knowledge, none of the previous studies used MoCA for cognitive screening of patients with cerebrovascular risk. Vascular causes of MCI have until recently been less well studied. For MCI patients with a marked cerebrovascular component, the term "MCI of the vascular type" can also be used [9]. Vascular risk factors have measurable negative effects on the brain and cognitive abilities [10]. Recent evidence also suggest that vascular MCI may be common and treatable [11–13]. In Sydney Stroke Study, the prevalence of vascular MCI 3–6 months after stroke was 36.7% and although subjects with VaD and vascular MCI did not differ from those with no cognitive impairment on any specific risk factor, those with impairment had greater number of vascular risk factors [14]. The presence of vascular risk factors may carry a long-term risk of cognitive impairment. In the past years major change has been the increasing recognition of mixed dementias, a state where vascular dementia coexist with other causes of dementia, particularly Alzheimer's disease [15]. Mixed vascular dementia and Alzheimer's disease may account for up to half of all dementias and may be more common than any other single group [16,17]. Recent data also show numerous similarities in vascular risk factors contributing to pathogenesis of both VaD and AD [18]. Recent studies mostly including post-stroke patients have demonstrated that many patients admitted for stroke seem to have had preexisting cognitive decline [19].

The primary aim of our study was to compare and to evaluate usefulness of two brief cognitive tests (MMSE and MoCA) in early detection of mild cognitive changes in patients with cerebrovascular risk factors present, including patients with first clinical signs of cerebrovascular disease (either with stroke or TIA) and asymptomatic subjects with one or more cerebrovascular risk factors present. The secondary aim was to determine the possible associations of specific vascular risk factors and cognitive results in individuals with symptomatic and asymptomatic cerebrovascular disease.

2. Materials and methods

2.1. Subjects

Two groups of participants were recruited from University Department of Neurology, Sestre milosrdnice University Hospital in Zagreb. The patients group (PG) consisted of 110 participants (mean age 56±7.0 years, 75 men, 35 women) admitted to the Department of Neurology due to first cerebrovascular incident (first-ever ischemic stroke or TIA). Control subjects group (CG) consisted of 45 subjects (mean age 53±6.0 years, 22 men, 23 women) who were treated at the Department of Neurology as outpatients and had no clinical signs of cerebrovascular disease but had one or more vascular risk factors present. In PGs, stroke was diagnosed by an experienced neurologist according to clinical signs (sudden onset of weakness or paralysis, numbness or tingling, speech disturbances, loss of vision or double vision) and was also corroborated by CT finding, while TIA was diagnosed according to redefined diagnostic criteria of the TIA Working Group [20]. Inclusion criteria for PGs were: first-ever ischemic cerebral stroke or TIA, age>45 years and no other neurological or psychiatric disorder. Aphasic individuals and individuals with MMSE score≤20 were not included in order to retain a group of subjects who could be reliably tested. Exclusion criteria for both groups were subjective or objective memory complaints prior to enrollment. All participants from PG and CG came from the same rural origin.

2.2. Cognitive testing

2.2.1. Standard MMSE

This is a popular mental status test which is widely used for cognitive assessment. Total MMSE score from 25 to 30 is considered normal, while scores below 24 points indicate dementia [5,21].

2.2.2. MoCA

This is a 30-point test covering eight cognitive domains (Table 1) [8]. MoCA was translated to Croatian and was administered according to administration and scoring instructions given by the authors [8]. Previous study indicated that participants with 12 years of education or less had worse performance on MoCA, so 1 point was added to their total MoCA score (if total MoCA score<30) [8]. MoCA scores below 26 points are considered abnormal [8].

After giving informed consent, all subjects were tested using standard MMSE [5] and Montreal Cognitive Assessment (MoCA) [8] at baseline visit and at three- and six-

Table 1
Cognitive domains covered by MoCA [8]

Montreal Cognitive Assessment (MoCA)		
Cognitive functions	Task	Points
	– Clock-drawing	3
Visuospatial abilities	– Three-dimensional cube copy	1
	– Alteration task (adapted from the Trial Making B Task)	1
	– Two-item verbal abstraction task	2
Executive functions	– Phonemic fluency task	1
	– Confrontation naming task	3
Language	– Repetition (two syntactically complex sentences)	2
Attention	– Sustained attention task (target detection using tapping)	1
Concentration	– Serial subtraction task	3
Working memory	– Digits forward and backward	2
Memory	– Short-term memory recall task	5
Orientation	– Orientation to time and place	6

month points. Baseline cognitive testing in PGs was performed immediately upon admission or at the latest 48 h afterwards the cerebrovascular incident occurred. In CGs, baseline testing was done during initial visit to outpatient's clinic.

2.3. Clinical work-up

In all subjects data on conventional vascular risk factors were assessed prior to baseline cognitive testing, including data on age and sex, arterial hypertension, diabetes, hyperlipoproteinaemia, cigarette smoking and obesity. Additional data were collected on cardiovascular risk factors/diseases (CVD), including coronary heart disease, congestive heart failure, peripheral vascular disease, left ventricular hypertrophy, cardiac arrhythmias and atrial fibrillation. In all subjects standard CDFI of common carotid arteries (CCA), internal carotid arteries (ICA) and external carotid arteries (ECA) with intima–media thickness (IMT) measurement of extracranial carotid arteries was done on admission. IMT is considered to be an independent vascular risk factor [22]. The predictive value of IMT with regards to cardiovascular complications has been established in several prospective studies and suggests that IMT measurement may participate in the future in the stratification of vascular risk of asymptomatic patients in primary prevention [22,23]. IMT was measured in the near and far walls of the three main segments of extracranial carotid arteries (CCA, carotid bifurcation and ICA) on both sides [22,24]. For each segment, ultrasound scan was performed in more than one direction, the maximum value of IMT is selected, and the final IMT considered is the average of IMT values at the 12 sites examined. Measurements of IMT were done on the basis of video image by visual assessment of the leading edges (the upper demarcation line) of the blood-intima and media–adventitia interfaces defining IMT. The analysis was performed off-line manually with the assistance of a computerised program, by placing a cursor on the interfaces in the digitalised video image [22,23]. IMT values above 0.8 mm were considered pathological [25]. CDFI and IMT measurements were done on commercially available equipment (Aloka Prosound SSD-550) with linear 8 MHz transducer.

We also used transcranial Doppler sonography (TCD) for measurement of mean blood flow velocity (MBFV) values in basal cerebral arteries as a non-invasive and simple diagnostic tool for assessment of cerebral hemodynamics [26].

In all participants transcranial Doppler sonography (TCD) was performed on commercially available equipment (TCD DWL Multidop X4 instrument) with a 2 MHz hand-held pulsed wave Doppler probe. Transtemporal approach was used in order to evaluate cerebral hemodynamics of the circle of Willis while subforaminal approach was used for insonation of terminal vertebral and basilar arteries. The key flow parameters which include the mean flow velocity (MFV), pulsatility index (PI) and direction of flow in the ophthalmic artery, were recorded for each participant and side, according to well defined diagnostic protocol [27]. Although the cerebral perfusion is largely influenced by other co-factors such as colateral flow, anatomical variations of the circle of Willis, the status of extracranial arteries etc., previous studies showed that mean blood flow velocities (MBFV) measured by TCD indirectly indicate the hemodynamics of the basal cerebral arteries [27,28]. TCD findings were interpreted and classified as normal or not normal according to previously published criteria [29].

All Doppler ultrasound examinations (CDFI of carotid arteries with IMT measurement and TCD) were done and interpreted by experienced physician trained in Doppler ultrasound assessment.

All PGs underwent computed tomography (CT) scan of the brain within 24 h after admission. CT images were acquired according to standard protocol (unenhanced scans with a slice thickness of 5 mm) on a «Siemens-Sensation» Multislice Computed Tomography (MSCT) scanner with 16-row detector layer. Brain CT findings were interpreted by experienced physician trained in neuroradiology blinded to previously assessed data, and were classified as positive if signs of ischemic stroke were present as was previously described elsewhere.

2.4. Statistical analysis

Prior to any further analysis, all data sets were analysed for normality using Kolmogorov–Smirnov test, and are presented as median ± interquartile range (IQ) for data that were not-normally distributed and mean ± standard deviation for data that were normally distributed.

Normally distributed data sets were analysed using Student's *t*-test, and not-normally distributed data sets were analysed using Mann–Whitney Rank Sum Test and Kruskal–Wallis One Way Analysis of Variance on Ranks (ANOVA on Ranks), post hoc analysis was performed using multiple comparison procedures (Dunn's method). Difference was considered to be statistically significant at $p < 0.05$. In order to compare overall cognitive decline measured by MMSE and MoCA for both PGs and CGs over the six-month period, Δ values were calculated for MMSE (MMSE in–MMSE 6) and MoCA scores (MoCA in–MoCA 6) and were presented as ΔMMSE and ΔMoCA and used for further calculations. ΔMMSE and ΔMoCA scores were also calculated for subgroups of PGs and CGs with different vascular risk factors.

All statistical procedures were done using statistical software SigmaStat 3.0, SPSS Inc.

3. Results

Basic demographic variables, mean MMSE and MoCA scores for the three measurements and the vascular risk factors profile of subjects according to the National Stroke

Association (NSA) Stroke Prevention Guidelines, with addition of data on IMT values and recordings of multiple risk factors (MRF>2) data for both PGs and CGs are presented in Table 2.

Both PGs and CGs were sex, age and education level matched. In 70.9% (78) of patients versus 53.3% (24) controls multiple risk factors were present. Asymptomatic subjects (CGs) most often had arterial hypertension ($n=22$, 48.8%), hyperlipoproteinaemia ($n=19$, 42.2%) and diabetes mellitus ($n=16$, 35.5%) while PGs most often had arterial hypertension ($n=67$, 60.9%), hyperlipoproteinaemia ($n=60$, 54.5%) and increased IMT values ($n=55$, 50%). There was no statistically significant difference in proportions of specific vascular risk factors, except for increased IMT values ($p=0.049$).

3.1. Cognitive results assessed by MMSE and MoCA

A cutoff score of 26 was used for MoCA and for MMSE a cutoff score of 24 was used [5,6,8]. Statistically significant differences in median cognitive scores for patients with stroke or TIA and for symptoms-free controls during the six-month follow-up period were found when either MMSE or MoCA was used for cognitive assessment (Table 2).

As demonstrated by the median box plots in Figs. 1 and 2, initially normal median MMSE scores of both PGs and CGs remained within normal range after three and after six consecutive months. When MoCA was used, the initial median scores for both groups were normal as well. In PGs, median MoCA scores after three and after six consecutive months were below normal range (<26 points). In CGs, after 3 months median MoCA score was at cutoff score (median 26.0; IQ range 25.0–27.0), dropping at clearly abnormal values 6 months after initial testing (median 24.0; IQ range 23.0–26.0).

As seen in Figs. 1 and 2, overall cognitive performance on MMSE for both groups throughout the study period fell within the normal range but the administration of MoCA revealed discrete cognitive abnormalities — after 3 months only in PGs, and after 6 months in PGs and also in CGs.

The rate of cognitive decline calculated as ΔMMSE during the six-month study period was analysed for PGs

Table 2
Basic demographic variables, median MMSE and MoCA scores for the three measurements and the vascular risk factors profile of the subjects

	PG	CG	*p*
Participants (*N*)	110	45	
Cerebrovascular disease (stroke/TIA), *N*	84/26	–	
Females, *N*/%	35/43	23/51	0.465
Education level (mean/SD) years	11.2/4.12	12.08/3.28	0.126
Age (mean/SD) years	55.6/7.48	53.3/6.05	0.069
MMSE in score (median; interquartile range)	28; 26–29	29; 28–30	<0.001 [a]
MMSE 3 score (median; interquartile range)	26; 25–27	28; 27–29	<0.001 [a]
MMSE 6 score (median; interquartile range)	25; 24–26	27; 26–28	<0.001 [a]
MoCA in score (median; interquartile range)	26; 25–28	29; 26.5–30	<0.001 [a]
MoCA 3 score (median; interquartile range)	23; 21–25	26; 25–27	<0.001 [a]
MoCA 6 score (median; interquartile range)	20; 17–21	24; 23–26	<0.001 [a]
Arterial hypertension, *N*/%	67/60.9	22/48.8	0.229
Hyperlipoproteinaemia, *N*/%	60/54.5	19/42.2	0.225
Diabetes mellitus, *N*/%	24/21.8	16/35.5	0.117
Obesity, *N*/%	33/30	9/20	0.284
Previous/current smoking, *N*/%	44/40	15/33.3	0.550
Coronary disease, *N*/%	34/30.9	7/15.5	0.076
Atrial fibrillation, *N*/%	27/24.5	9/20	0.694
Increased IMT (>0.8 mm), *N*/%	55/50	14/31.1	0.049 [a]
Multiple risk factors (>2), *N*/%	78/70.9	24/53.3	0.056

[a] Differences are statistically significant.

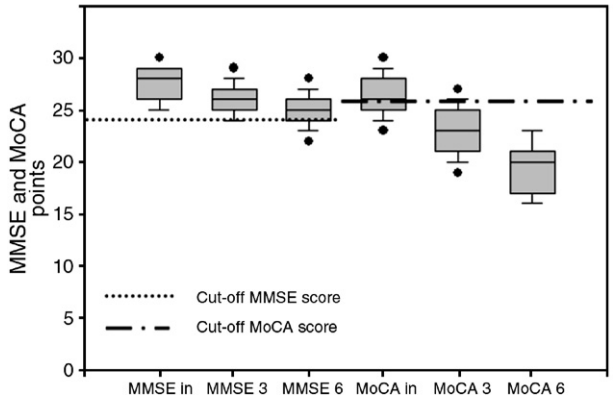

Fig. 1. Cognitive testing in patients group: MMSE and MoCA on the baseline (initial) testing (MMSE in, MoCA in), after 3 months (MMSE 3, MoCA 3) and after 6 months (MMSE 6, MoCA 6) shown on a box plot presenting median values, 10th, 25th, 75th and 90th percentiles as vertical boxes with error bars.

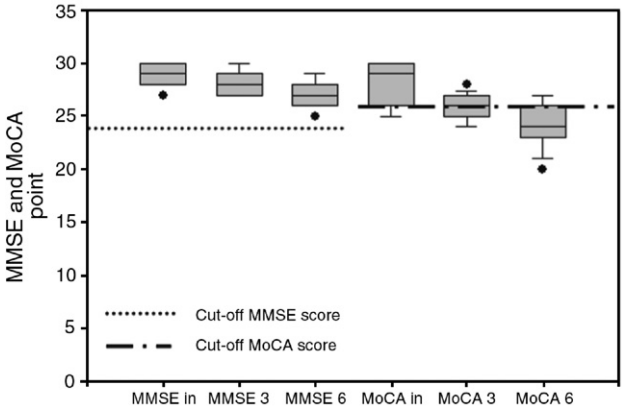

Fig. 2. Cognitive testing in control group: MMSE and MoCA on the baseline (initial) testing (MMSE in, MoCA in), after 3 months (MMSE 3, MoCA 3) and after 6 months (MMSE 6, MoCA 6) shown on a box plot presenting median values, 10th, 25th, 75th and 90th percentiles as vertical boxes with error bars.

Table 3
Cognitive scores assessed by MMSE and MoCA in PGs and CGs at initial testing (in.) and at 3 and 6 month points, proportions (percentages) of subjects without (w/o) and with (w) cognitive impairment

	in.		3 months		6 months	
	w/o	w	w/o	w	w/o	w
PG						
MMSE	93 (88.2)	17 (15.4)	74 (67.3)	36 (32.7)	63 (57.2)	47 (42.7)
MoCA	64 (58.2)	46 (41.8)	27 (24.5)	83 (75.5)	18 (16.4)	92 (83.6)
CG						
MMSE	45 (100)	0 (0)	43 (95.5)	2 (4.4)	42 (93.3)	3 (6.6)
MoCA	39 (86.6)	6 (13.3)	35 (77.7)	10 (22.2)	30 (66.6)	15 (33.3)

(median 2.0, range 2.0–4.0) and CGs (median 2.0, range 1.0–3.0) showed statistically significant difference ($p=0.022$), which can probably be explained by differences in data range and distribution. Likewise, when the rate of cognitive decline during the six-month study period was calculated as ΔMoCA for PGs (median 7.0, range 5.0–8.0) and CGs (median 4.0, range 3.0–5.0) differences were also found to be statistically significant ($p<0.001$).

Percentages of PGs and CGs with and without cognitive impairment when assessed by MMSE or by MoCA during the study follow-up period of 6 months are summarised in Table 3.

In PGs MMSE showed 15.4% cognitively impaired subjects at initial testing, versus 41.8 when MoCA was used. After the six-month follow-up period, we found 42.7% cognitively impaired subjects in PG using MMSE, versus 83.6% when MoCA was used.

At initial testing, MoCA scores in 13.3% CGs were below normal range, while MMSE scores in all CGs were normal. After 6 months, MMSE scores were below normal range in 6.6% CGs; MoCA scores were below normal range in 33.3% CGs.

When ΔMoCA values in subgroup of PGs with stroke (median 7.0 range 6.0–8.0) were compared to ΔMoCA values in PGs with TIA (median 5.0, range 5.0–6.0) statistically significant difference was found ($p<0.001$). ΔMMSE values for PGs with stroke (median 2.5, range 1.5–4.0) and ΔMMSE values for PGs with TIA (mean 2.0, range 2.0–3.0) did not differ significantly ($p=0.203$).

Differences between ΔMoCA in PGs with TIA and ΔMoCA in CGs were not statistically significant ($p=0.053$).

Table 4
Differences in cognitive decline assessed by MMSE (ΔMMSE) in subgroups of PGs and CGs with different vascular risk factors present (+) or absent (−)

ΔMMSE								
CV risk factors	PG				CG			
	Median	25%	75%	*p*	Median	25%	75%	*p*
AH +	2.0	1.0	3.0	0.510	2.5	2.0	3.0	0.003 [a]
AH −	3.0	2.0	4.0		1.0	1.0	2.0	
Hyperlipoproteinaemia +	2.5	1.0	3.0	0.909	2.0	1.0	3.0	0.670
Hyperlipoproteinaemia −	2.0	2.0	4.0		2.0	1.0	3.0	
DM +	3.0	1.5	4.0	0.244	2.0	1.0	3.0	0.924
DM −	2.0	2.0	3.0		2.0	1.0	3.0	
Obesity +	3.0	1.75	4.0	0.527	1.0	0.75	3.0	0.132
Obesity −	2.0	1.75	3.0		2.0	1.0	3.0	
Smoking +	2.5	2.0	4.0	0.280	2.0	1.25	2.75	0.952
Smoking −	2.0	1.0	3.0		2.0	1.0	3.0	
Coronary disease +	3.0	2.0	4.0	0.208	1.0	1.0	2.0	0.085
Coronary disease −	2.0	1.0	3.0		2.0	1.0	3.0	
AF +	3.0	2.0	4.0	0.089	2.0	1.0	2.0	0.560
AF −	2.0	1.0	3.0		2.0	1.0	3.0	
IMT>8 mm +	2.0	1.0	3.0	0.375	3.0	2.0	3.0	<0.001 [a]
IMT>8 mm −	3.0	2.0	4.0		2.0	1.0	2.0	
MRF (>2) +	3.0	2.0	4.0	0.034 [a]	–	–	–	0.062 (*t*-test)
MRF (>2) −	2.0	1.0	3.0		–	–	–	
Abnormal TCD findings +	3.0	2.0	4.0	0.054	2.5	2.0	3.0	0.103
Abnormal TCD findings −	2.0	1.0	3.0		2.0	1.0	2.25	
(AH+IMT>8 mm) +	2.0	1.0	3.0	0.234	3.0	2.0	3.0	0.079
(AH+IMT>8 mm) −	3.0	2.0	4.0		2.75	2.0	3.0	
(AH+MRF>2) +	2.0	1.25	4.0	0.534	3.0	2.0	3.0	0.087
(AH+MRF>2) −	2.0	1.5	4.0		2.5	1.75	3.0	

Mann–Whitney Rank Sum Test, *t*-test.
AH — arterial hypertension.
DM — diabetes mellitus.
AF — atrial fibrillation.
IMT>8 mm — increased IMT values.
MRF — multiple risk factors.
[a] Statistically significant difference.

3.2. Relationship of cerebrovascular disease, vascular risk factors and cognitive performance

For both PGs and CGs ΔMMSE and ΔMoCA values were analysed separately for subgroups of subjects with specific vascular risk factors present (arterial hypertension, hyperlipoproteinaemia, diabetes, obesity, previous or current smoking, coronary disease, atrial fibrillation, increased IMT values) and for subgroups of subjects with multiple risk factors (MRF>2) and abnormal TCD findings. In PGs, analysis of ΔMMSE and ΔMoCA values was also performed separately for subgroups of subjects with first-ever stroke and for subjects with TIA.

When MMSE was used, subgroup of PG with multiple risk factors showed statistically significant cognitive decline compared to PGs with only one or two risk factors present ($p=0.034$). In CGs, ΔMMSE showed statistically significant difference in individuals with arterial hypertension ($p=0.003$) and increased IMT values ($p<0.001$) (Table 4).

When MoCA was used, statistically significant cognitive decline was found for subgroup of PGs with multiple risk factors (MRF>2) compared to PGs with only one or two risk factors present ($p=0.002$) and for PGs with abnormal TCD findings compared to those with normal TCD findings ($p<0.001$). In CGs, ΔMoCA showed statistically significant difference in individuals with simultaneously present combination of arterial hypertension and increased IMT values ($p<0.001$) and with simultaneously present arterial hypertension and multiple risk factors ($p=0.003$) (Table 5).

4. Discussion

In our study, cognitive decline was shown earlier when MoCA was used for assessment. When initially tested using MMSE, 15.5% patients with first-ever cerebrovascular incident (either stroke or TIA) scored below normal range, versus 41.8% when MoCA was used. Likewise, 6 months after cerebrovascular incident, scores below normal range were found in 42.7% patients using MMSE and even in 83.6% on the MoCA. This finding can be compared to the results presented by the authors of MoCA who found that 73% of individuals with MCI scored in abnormal range on the MoCA but in the normal range on the MMSE [8]. In their study, differences between the groups of cognitively normal

Table 5
Differences in cognitive decline assessed by MoCA (ΔMoCA) in subgroups of PGs and CGs with different vascular risk factors present (+) or absent (−)

ΔMoCA								
CV risk factors	PG				CG			
	Median	25%	75%	*p*	Median	25%	75%	*p*
AH +	7.0	5.0	8.0	0.983	–	–	–	0.136 (*t*-test)
AH −	7.0	6.0	8.0		–	–	–	
Hyperlipoproteinaemia +	7.0	6.0	8.0	0.174	4.0	3.0	4.0	0.605
Hyperlipoproteinaemia −	6.0	5.0	8.0		4.0	3.0	5.0	
DM +	7.0	6.5	9.0	0.057	4.0	3.0	5.5	0.250
DM −	7.0	5.0	8.0		4.0	3.0	4.0	
Obesity +	7.0	6.0	8.0	0.201	4.0	2.75	4.5	0.639
Obesity −	7.0	5.0	8.0		4.0	3.0	5.0	
Smoking +	7.0	5.0	8.0	0.619	4.0	3.0	4.0	0.772
Smoking −	7.0	5.0	8.0		4.0	3.0	5.0	
Coronary disease +	7.0	5.0	8.0	0.441	3.5	3.0	5.0	0.676
Coronary disease −	7.0	5.0	8.0		4.0	3.0	4.75	
AF +	7.0	5.0	8.0	0.372	4.0	3.0	4.0	0.469
AF −	7.0	5.0	8.0		4.0	3.0	5.0	
IMT>8 mm +	7.0	5.0	8.75	0.071	4.0	3.0	4.0	0.564
IMT>8 mm −	7.0	5.0	7.75		4.0	3.0	5.0	
MRF (>2) +	7.0	6.0	8.0	0.002 [a]	4.0	3.0	4.0	0.741
MRF (>2) −	6.0	5.0	7.0		4.0	3.0	5.0	
Abnormal TCD findings +	7.0	6.0	9.0	<0.001 [a]	4.0	3.0	4.0	0.480
Abnormal TCD findings −	6.0	5.0	7.0		4.0	3.0	5.0	
(AH+IMT>8 mm) +	7.0	5.0	8.0	0.385	4.0	3.0	4.0	<0.001 [a]
(AH+IMT>8 mm) −	7.0	5.25	7.75		1.0	1.25	2.75	
(AH+MRF>2) +	7.0	5.3	8.0	0.069	4.0	3.0	5.0	0.003 [a]
(AH+MRF>2) −	7.0	5.1	7.75		2.75	2.0	6.0	

Mann–Whitney Rank Sum Test, *t*-test.
AH — arterial hypertension.
DM — diabetes mellitus.
AF — atrial fibrillation.
IMT>8 mm — increased IMT values.
MRF — multiple risk factors.
[a] Statistically significant difference.

individuals, subjects with MCI and subjects with AD were much more pronounced using the MoCA than the MMSE [8]. We observed the decrement in cognitive performance during the six-month study period in both patients with stroke/TIA and in symptoms-free controls with CV risk factors which was more evident if MoCA ($p<0.001$) than if MMSE was used ($p=0.022$). However, we have found a 2-point median decrease during the follow-up period for both tests, so median cognitive scoring results for both groups are overlapping, although distinctively because the data ranges are quite different (5.0–8.0 for patients and 3.0–5.0 for controls).

A proportion of cognitively impaired patients 6 months after stroke that we observed is relatively large compared to the results previously assessed by other authors (6 months after first stroke or TIA 83.6% patients scored below normal range on the MoCA). The other studies investigating cognitive performance after stroke found different rates of cognitive decline, but mainly classified as dementia [14,30–34]. In a study by Barba et al. 30% of patients with stroke were diagnosed with dementia 3 months after stroke [30]. Zhou et al. found an incidence of dementia 3 months following first-ever stroke of 22.7% [31] and results from the Sydney Stroke Study showed prevalence of VaMCI in patients following ischemic stroke after three to 6 months to be 36.7% [14]. Tatemichi et al. found that 26.3% of stroke patients were classified as "demented" 3 months after stroke [32] and in the study by Rasquin et al. performed in a larger cohort of 196 stroke patients, 6 months after stroke, MCI was diagnosed in 61.3% patients, 7.7% had VaD, while 18.6% had no cognitive problems [33]. Most of these studies included older subjects when compared to our sample. However, in a research by Madureira et al. performed in 237 stroke patients of similar age (mean 59±12.7 years) 3 months after stroke cognitive impairment was common, while dementia was infrequent [34].

The higher percentage of patients scoring below normal range on cognitive tests in our study could be due to the fact that we aimed only to recognise the existence of cognitive deficits. Our aim was not to determine and to classify the severity of cognitive decline or to define the diagnosis of dementia in our subjects. Thus our findings probably reflect a certain number of patients with more severe degree of post-stroke cognitive decline as well as those with MCI. It is also possible that some of the patients from our sample already had preexisting slight cognitive changes before stroke or TIA occurred, though we have tried to eliminate that possibility during the recruitment. One earlier study showed that one sixth of stroke patients have preexisting dementia [35]. Dementia post-stroke may be a result of cumulative effect of vascular as well as degenerative changes [35]. It appears that a wide spectrum of cognitive problems after stroke occurs far more frequently than is usually considered.

In our study 13.3% symptoms-free controls scored below normal range on the MoCA on initial testing, with the increase to 33.3% after 6 months. The patients and controls from our sample were matched considering basic demographic variables of sex, age and education levels as well as for the vascular risk profile (with the exception of increased IMT values). Considering this, cognitive results of our controls could as well be similar to those in subjects if they were tested before stroke or TIA occurred. Other studies have reported the incidence of cognitive decline before stroke to be from 16.3 to 40% [19].

Previous longitudinal studies that mostly used MMSE as a screening instrument indicated that cognitive deficits may be present during the years before a diagnosis of vascular dementia is established [36–39]. Meyer et al. reported faster cognitive decline during the six-month period in cognitively impaired persons who developed VaD an average of 4 years later, compared with a group with stable cognitive impairment [38]. Laukka et al. observed preclinical cognitive deficits preceding VaD during the six-year period and found no MMSE deficits 6 years before the diagnosis, but 3 years before the occurrence of VaD poor MMSE scores were significantly related to the future dementia [39]. In our study, MoCA scores showed that one-third of individuals with increased vascular risk but without stroke or TIA had cognitive impairment after the six-month follow-up period. Although those individuals most likely appear to be candidates for the manifestation of cerebrovascular disease, either clinically significant vascular dementia or/and stroke/TIA, such a statement would be rather speculative. We must stress that other factors, such as duration of exposure to specific vascular factors or the influence of potential treatment and control of risk factors were not assessed in our study. However, we believe that in this particular group of individuals preventative measures aimed at strong medical management of risk factors would probably beneficially affect occurrence of further cognitive decline.

In our study, MoCA also showed significant differences between the rates of cognitive decline in PGs with stroke versus PGs with TIA ($p<0.001$) while no significant differences were found when rates of cognitive decline between PGs with TIA and CGs were compared ($p=0.053$). This observation may be due to possibly present silent ischemic lesions in clinically asymptomatic controls as has been previously reported by other authors [40].

Recent studies suggest that cerebrovascular risk factors are strongly associated with dementia of both vascular or Alzheimer's type [41]. Vascular dementia is known to be preceded by several years of exposure to vascular risk factors [42]. According to latest studies common risk factors for AD and VaD include age, family history of dementia, previous TIA or stroke, atherosclerosis with coronary heart disease, increased or low systemic blood pressure, diabetes type II, hypercholesterolaemia, hyperhomocystinemia, smoking and presence of apolipoprotein E epsilon 4 (apoE4) allele [41]. Other authors found the risk of conversion of MCI to dementia to be associated with atrial fibrillation, elevated blood pressure and pulse pressure as well as elevated plasma cholesterol levels [43–47].

In our study, positive associations for cognitive decrement and multiple CV risk factors (>2) were found in PGs ($p=0.034$ for MMSE; $p=0.002$ for MoCA). In CGs, positive associations were found for cognitive decrement and arterial hypertension with increased IMT values ($p<0.001$ for MMSE) and for multiple CV risk factors and arterial hypertension ($p=0.003$ for MoCA).

It was shown that long-standing hypertension may affect the media and thicken the vessel walls, impairing the capacity of small blood vessels to dilate in response to increased need for blood supply [48]. Study by Farkas et al. previously showed that insufficient blood flow leads to decreased glucose metabolism which has negative effects on cognitive functioning [49]. Impaired autoregulation of blood flow may also contribute to development of ischemic white matter lesions [49].

In PGs, significant differences were found for subgroups of PGs with stroke/stroke with MRF/TIA and TIA with MRF. It appears that multiple risk factors (>2) may have a strong influence on cognitive performance in individuals with symptomatic cerebrovascular disease. This finding should be interpreted with caution because the profile of multiple risk factors in our study was not separately analysed due to relatively small sample involved in the study. More research, including longitudinal, population based studies would be necessary in order to exactly determine the possible influence of particular multiple risk factors patterns and cognitive performance. However, this finding is in line with the reports from the Sydney Stroke Study stating that although subjects with VaD and vascular MCI did not differ from those with no cognitive impairment on any specific risk factor, those with impairment had greater number of vascular risk factors [14]. Similarly, Kivipelto et al. found the risk of Alzheimer's disease in later life to be increased if combination of raised systolic blood pressure and high serum cholesterol concentration is present in midlife [44].

Marked decrease in cognitive scores that we registered not only in patients, but also in asymptomatic controls could probably be explained by population characteristics. It should be noted that subjects in the control group and patients with symptomatic cerebrovascular disease were matched according to the presence of existent vascular risk factors, with the exception of increased IMT values which were more often present in the patients group ($p=0.049$). Considering marked decrement in cognitive scores we observed in symptoms-free controls with vascular risk factors present, we believe that there is also a possibility that those individuals might have suffered silent stroke or strokes prior or during the study follow-up period. One shortcoming of our study is the fact that no neuroimaging (CT scan) was performed in controls, so possible preexistent brain damage in this group could not have been evaluated. Additional possible explanation for the marked cognitive decrement assessed in both PGs and CGs could be the fact that the study assessor was not blinded for the subjects of the study, which might have influenced the results. The same rural origin of PGs and CGs probably also implicates the results. However, homogene structure of the subjects in our sample may also be considered one advantage of the study, while other studies mostly observed groups of subjects that were more heterogenous considering demographic variables. Another advantage could be the fact that initial testing in patients group took place almost immediately after stroke or TIA occurred (within 48 h), while in most studies first cognitive assessment was performed 3 months after stroke. It should be noted that our aim was not to assess specificity and sensitivity of MoCA in detecting discrete cognitive decline of vascular type, but our results only implicate usefulness of MoCA as a rapid screening technique in this homogene patients group with potential cognitive problems.

As vascular pathology appears to be a common characteristic of both VaD and AD, the importance of early and accurate diagnostics of mild cognitive decline is emphasized in order to recognise the patients in whom strong medical control of vascular risk factors could prevent or at least delay clinically evident dementia of any type. Our study is consistent with today's research which moves towards the early identification of subjects at the presymptomatic stage, which has been termed «brain-at-risk» and is the most appropriate for early primary and secondary preventative therapy [50].

We can conclude that the use of MoCA could aid to early recognition of discrete cognitive disturbances in both symptomatic and asymptomatic individuals with increased CV risk. As a brief screening method, MoCA could be routinely used in clinical setting for early identification and follow up of apparently mentally healthy individuals with vascular risk factors and subtle pre-stroke cognitive decline in whom preventative measures could be applied. In addition to previously well defined single defined risk factors, the presence of multiple risk factors seems to be associated with increased risk of cognitive decline. As our study may have some selection and assessment biases, further studies focusing on the potential interactive effect of vascular risk factors on cognitive performance would be necessary to corroborate the present findings.

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