ORIGINAL RESEARCH

Neuropsychological and neuroimaging markers in prediction of cognitive impairment after ischemic stroke: a prospective follow-up study

Shima Mehrabian[1]
Margarita Raycheva[1]
Neli Petrova[2]
Armina Janyan[3,4]
Mariya Petrova[1]
Latchezar Traykov[1]

[1]Clinic of Neurology, University Hospital Alexandrovska, Sofia, [2]Clinic of Neurology, MHAT "Ruse", Ruse, [3]Research Center for Cognitive Science, Department of Cognitive Science and Psychology, New Bulgarian University, Sofia, Bulgaria; [4]Laboratory for Cognitive Studies in Language, National Research Tomsk State University, Tomsk, Russia

Correspondence: Latchezar Traykov
Clinic of Neurology, University Hospital Alexandrovska, 1 Georgi Sofiiski Street, 1431 Sofia, Bulgaria
Tel +359 2 923 0752
Fax +359 2 952 0427
Email traykov_l@yahoo.fr

Background: There are few longitudinal studies with controversial results examining delayed changes in cognition after ischemic stroke and predictive values of neuropsychological and neuroimaging markers.

Objective: The objectives of this study were to evaluate the delayed changes in cognition in poststroke patients and their relationship to the neuropsychological and neuroimaging markers measured during the acute poststroke phase.

Methods: Eighty-five first-ever stroke inpatients (mean age 65.6±5.6 years) without previous cognitive complaints were prospectively evaluated with a comprehensive neuropsychological battery at the 5th day and the 1st, 6th, and 12th months. A wide range of clinical, radiological, and neuropsychological variables were examined.

Results: Our results showed significantly poorer performance on mini–mental state examination, memory, attention/executive functions, and processing speed in patients with stroke in comparison with stroke-free cognitively intact controls. Multiple regression analysis revealed that hippocampal atrophy is the strongest predictor of delayed cognitive impairment. Secondary divided subgroups according to Isaacs Set Test (IST) score showed that patients with IST score ≤28 had different patterns of cognitive and neurological impairment after 1 year. Baseline impairments in attention/executive functions and memory were associated with development of dementia in poststroke patients.

Conclusion: Executive functioning deficit appears to have a predictive power for cognitive impairment progression. The study suggests that IST as a screening test has a potential to be a reliable and quick tool for poststroke cognitive impairment evaluation and delayed cognitive and neurological outcome. Hippocampal atrophy was the strongest predictor for cognitive impairment outcome, even in poststroke cognitive impairment. The findings may set the stage for better poststroke management.

Keywords: hippocampal atrophy, IST, neuropsychological predictors, poststroke dementia

Introduction

Poststroke cognitive impairment is frequent. There are, however, few longitudinal studies examining delayed changes in cognition, and predictive values of neuropsychological and neuroradiological markers.[1–5] In community-based studies, the prevalence of poststroke dementia (PSD) is approximately 30% and the incidence of new-onset dementia after stroke increases from 7% after 1 year to 48% after 25 years.[6] Some studies indicate that PSD may be reversible in a substantial proportion of patients.[5] In contrast, other studies found that not only is the risk of PSD high immediately after stroke but it also remains higher in nondemented patients 3 months after the stroke.[1] There is a need to identify individuals at particular risk of poststroke cognitive decline,

and hence to target interventions for secondary prevention and improve the outcome and quality of life of stroke patients.

Identifying poststroke cognitive impairment at an early stage might increase the possibility of reducing or even preventing further cognitive decline. Few studies have examined the prognostic value of these impairments at a poststroke early stage.[7] Identifying a quick neuropsychological screening tool which could predict delayed cognitive and functional decline in stroke patients is a challenge. The role of neuroimaging markers including white matter changes (WMC) and medial temporal lobe atrophy (MTLA) as a contributor to poststroke cognitive decline is still controversial.[8]

We present results from a prospective, hospital-based study of consecutive, first-ever stroke patients, designed to evaluate the delayed changes in cognition and their relationship to neuropsychological and neuroimaging markers. The study aimed to determine a quick cognitive screening test and neuroimaging markers measured in the acute poststroke phase which can accurately predict delayed cognitive and functional decline in poststroke patients.

Material and methods

Included in this study were consecutive inpatients with a first-ever ischemic cerebral stroke, aged 50–80 years, within 3 days of stroke onset. Patients were recruited from the acute stroke unit of the Clinic of Neurology, Ruse, Bulgaria. Stroke was defined as acute onset of focal neurological deficits attributable to cerebrovascular disease and documented by computerized tomography (CT).

Inclusion criteria for the study were: 1) Bulgarian ethnicity; 2) well-documented clinical presentation and CT scan of the brain; 3) ability to give informed consent or the availability of relative/caregiver to give proxy consent to participate in the study; and 4) availability of caregiver to give informed knowledge of the patients' earlier and current cognitive functioning.

Exclusion criteria included: 1) patients with a primary hemorrhagic stroke (intracerebral or subarachnoid); 2) history of any preceding cerebral vascular event; 3) patients with National Institutes of Health Stroke Scale (NIHSS) score >6; 4) persistent disturbed level of consciousness; 5) persistent aphasia; 6) history of prestroke cognitive impairment; 7) brain ischemia due to cardiorespiratory arrest; 8) systemic diseases known to involve the central nervous system; 9) severe sensory impairment (blindness and deafness); 10) known malignant disease or other chronic disease with poor prognosis; 11) neurological conditions (ie, Parkinson's disease, epilepsy, and head injury); and

12) history of psychiatric conditions (ie, depression, alcohol, and drug dependence).

A standard stroke evaluation was conducted on 522 consecutive patients admitted to stroke unit: 85 met the selection criteria; eleven were lost for follow-up at 12 months.

We composed a control group of 25 normal control subjects (NCs), matched to the patients group according to their age and educational level. All subjects gave written informed consent for their participation in the study which was approved by the local ethics committee. The guidelines of the ethics committee were adhered to.

Assessments and data collection

A vascular neurologist conducted a thorough physical examination and reviewed the imaging data and medical records of potential participants to determine eligibility. Baseline demographic and clinical data were collected. Neurological and neuropsychological assessments were conducted by an experienced neurologist and neuropsychologist at baseline (5th day after stroke onset) and at 1st, 6th, and 12th months.

Demographic data including age, sex, and educational level were collected. All patients were subjected to cardiac examination that included an electrocardiogram and echocardiography of the heart. Assessment of neurological status was determined using NIHSS score.[9]

Neuroimaging characteristics

A non-contrast CT brain scan examination was done for all patients. For hippocampal rating, we used the scale described in detail by Scheltens et al.[10,11] In brief, it is a five-point scale of hippocampal atrophy (normal =0, severe atrophy =4). For periventricular changes (PVCs) and deep WMC, we used the scale of Scheltens[12] evaluating the presence and extent of PVCs and deep WMC in different anatomic regions with a 0-to-6-point scale. Wattjes et al[13] described excellent intraobserver agreement between CT and magnetic resonance imaging (MRI) for medial temporal atrophy (mean κ, 0.88 and 0.86 on the left and right sides of the brain, respectively) and substantial overall agreement concerning WMC (mean κ, 0.79) with published visual rating scales.

Cognitive and neuropsychiatry assessments

A set of standardized neuropsychological tests sensitive for mild cognitive impairment (MCI) and covering major cognitive domains were selected.[14]

A detailed neuropsychological assessment was done four times for all patients, at the baseline (5th day of stroke onset)

and after 1, 6, and 12 months. Normative data for these tests were also established in the control group.

Several cognitive domains were assessed:

1) Global cognitive functioning using the standard mini–mental state examination (MMSE). In our study, we also used the scores of five MMSE subtests.

2) Learning and episodic verbal memory was assessed with list learning subtest from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery, using several measures: immediate recall (number of words recalled over three learning trials), delayed recall after 15 minutes delay, and recognition.

3) Attention was tested by the Trail Making Test, part A (TMT-A).

4) As a substantial part of executive functioning, we assessed cognitive flexibility/set shifting using TMT-B, and verbal fluency/set sifting using Isaacs Set Test (IST),[15] 15-second version. The IST assessed verbal fluency by measuring the ability to generate lists of words in four semantic categories (fruits, colors, cities, and animals) in a 15-second interval.[16] IST is considered as a brief screening timed cognitive test with highly loaded executive functioning (cognitive set shifting, generation, and processing speed) and semantic and working memory, found to be of predictive value for preclinical detection of dementia symptoms.

5) Language abilities were assessed by the 15-item subset of the Boston Naming Test.

6) Constructive praxis was evaluated by means of 4 Figures Coping Subtest from CERAD Neuropsychological Battery. The psychiatric evaluation included a semistructured interview and the 15-item Geriatric Depression Scale (GDS). Presence of depression was considered in participants with a GDS score more than 4. Independence level of everyday functioning was evaluated by Instrumental Activities of Daily Living (IADL)[17] with caregiver interview. Restriction in four IADL (telephone, transportation, medication, and finances) and depressive symptoms were examined at each follow-up visit.

In secondary analyses, we classified the stroke patients into two subgroups according to their IST score at baseline (groups at risk and normal limits [NL]) and compared their neuropsychological performance. We studied the pattern of neurological and cognitive changes in follow-up examinations in secondary subgroups.

The clinical and neuropsychological assessment of patients also included a diagnosis of no cognitive impairment (NCI), MCI, or presence of dementia at each time-point examination.

MCI was diagnosed using Winblad et al criteria[18] and objective cognitive impairment in one or more cognitive domains with a score of 1.0 standard deviation (SD) below the mean from the age-matched control population, while dementia was diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria[19] and National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.

Prospective follow-up assessments after 1, 6, and 12 months

All subjects were prospectively followed-up through the outpatient neurology clinic at 1st, 6th, and 12th months after stroke onset. Patients were similarly assessed, using the same battery of neuropsychological assessment, NIHSS, GDS, and IADL scale.

Statistical analysis

Data were expressed as mean ± SD. Calculations were done with the statistical package STATISTICA for Windows (version 8). A chi-square test was used for the group comparisons of qualitative variables and a one-way analysis of variance (ANOVA) or *t*-tests were performed for quantitative variables. Repeated measures ANOVA (rANOVA) was applied to trace the level of cognitive functions in time together with the ability of assessment types to differentiate between groups divided by IST score. Thus, only results with interactions were valued. Bonferroni post hoc test was applied when needed. Multiple regression analyses were used to assess the neuroimaging predictors for cognitive decline.

For all tests, values of $P<0.05$ were considered statistically significant.

Results

Patients and control demographic information is presented in Table 1. There was no difference in age or education level between strokes and controls. The final sample included 85 patients, 67 males and 18 females, with mean age 65.6±5.6 years (range: 50–80 years). The distribution of stroke lesions showed left middle cerebral artery lesions in 29 subjects, right middle cerebral artery lesions in 39 subjects, and vertebrobasilar lesions in 17 subjects. The mean score of NIHSS was 4.6±0.9 at the acute phase of stroke at baseline. Mild depression was present in 36.4% of stroke patients at baseline.

Table 2 presents the neuropsychological performance in controls and patients at baseline (5th day after stroke onset) and follow-up assessments. Stroke patients had significantly

Table 1 Baseline characteristics of patients and normal controls (NCs)

Baseline	NCs N=25	Poststroke patients N=85	Poststroke patients (NL) (IST >28) N=46	Poststroke patients (at risk) (IST ≤28) N=39
Age, years	64.1 (5.3)	65.6 (5.6)	64.5 (6.0)	66.6 (5.4)
Sex (male/female)	18/7	67/18	34/12	33/6
Education, years	11.7 (2.2)	11.3 (2.2)	11.5 (2.4)	11.0 (1.8)
MMSE	27.9 (1.4)	26.6 (2.3)***	27.3 (1.4)**	25.7 (2.7)
Diabetes (%)	4	28*	30	26
Hypertension (%)	76	86	85	87
NIHSS	0	4.6 (0.9)	4.6 (0.7)	4.7 (0.6)

Notes: Means are given with standard deviations in parentheses. A comparison (*t*-test) with control group was performed. *$P<0.05$; **$P<0.01$; ***$P<0.001$. Insignificant results are with $P>0.1$.
Abbreviations: IST, Isaacs Set Test; MMSE, mini–mental state examination; NCs, normal controls; NIHSS, National Institutes of Health Stroke Scale; NL, normal limits.

lower performance on most cognitive tasks at first evaluation. There were only two cognitive domains, language (Boston Naming Test) and praxis (figure copying), that were within the same range as controls.

The most significant differences between patients and NCs were found on tasks assessing orientation, executive functions, and memory. General cognitive functioning (MMSE) score at baseline assessment was significantly below the mean score of NCs. MMSE score was reduced because of mild anomia and orientation deficits in some of the scale items. Patients had significantly lower scores on all measures of verbal learning. Their performance was characterized by reduced short-term memory, slow learning, and lowered

level of recollection from long-term memory. Pattern of memory impairment resembled the one observed in medial temporal lobe dysfunction. The most significantly impaired were all timed tests of executive functioning – IST and TMT (A and B). All patients at baseline were cognitively slow, had noneffective set shifting, and reduced semantic generation.

Follow-up assessments revealed some changes in pattern of impairments, but the general cognitive functioning (MMSE) and executive functioning remained at significantly lower level of performance compared with NCs. Although patients gained better results in the 6th month assessment, they got worse results on cognitive testing as well as on functional scale of daily living activities 1 year after the stroke.

Table 2 Neuropsychological performance in NCs and patients at 5th day after stroke onset (baseline) and follow-up assessments

	NC	Stroke patients 5th day	Stroke patients 1st month	Stroke patients 6th month	Stroke patients 12th month
MMSE	27.9 (1.3)	26.6 (2.3)**	26.3 (2.8)**	26.9 (2.2)*	26.4 (2.8)*
• Orientation	10.0 (0.0)	9.7 (0.6)*	9.6 (1.0)*	9.7 (0.7)*	9.6 (0.8)**
• Memory	5.5 (0.7)	5.4 (0.8)	5.3 (0.9)	5.4 (0.8)	5.3 (0.9)
• Attention	4.4 (0.7)	4.1 (1.1)	4.0 (1.1)	4.2 (1.0)	4.0 (1.3)
• Language	7.1 (0.7)	6.6 (0.7)**	6.7 (0.7)*	6.9 (0.6)	6.8 (0.8)
• Praxis	0.9 (0.3)	0.8 (0.4)	0.7 (0.5)	0.8 (0.4)	0.7 (0.4)
IST	34.8 (3.1)	28.4 (5.9)***	28.5 (6.3)***	30.0 (5.7)***	29.4 (5.7)***
IADL (4 items)	0 (0)	0.2 (0.6)	0.6 (1.0)**	0.5 (0.9)**	0.7 (1.6)*
CERAD episodic memory – Immediate recall					
• I trial	4.0 (1.5)	3.0 (1.4)**	4.3 (1.5)	4.7 (1.7)⁻	4.6 (1.7)⁻
• II trial	6.6 (1.1)	5.1 (1.6)***	5.8 (1.6)*	6.0 (1.7)	6.1 (1.7)
• III trial	7.3 (1.1)	6.0 (1.6)***	6.3 (1.9)***	6.3 (1.6)***	6.6 (1.6)***
– Delayed recall	5.3 (1.6)	3.3 (2.2)***	4.4 (2.6)	4.7 (2.2)	5.2 (2.4)
– Recognition	18.7 (1.3)	16.6 (2.8)***	17.9 (2.3)⁻	18.0 (2.3)	18.3 (2.0)
TMT-A	57.3 (13.6)	98 (46)***	86 (41)***	80 (38)**	83 (44)**
TMT-B	111.7 (27.3)	209 (73)***	188 (81)***	174 (74)***	173 (77)***
BNT	14.6 (0.6)	14.1 (1.1)⁻	14.5 (0.9)	14.6 (0.7)	14.6 (0.7)
Figure copying	10.5 (0.7)	10.2 (1.1)	10.3 (1.1)	10.2 (1.1)	10.2 (1.0)
GDS	3.4 (2.0)	4.2 (3.2)	4.2 (3.1)	3.8 (3.4)	3.8 (3.5)

Notes: Means are given with standard deviations in parentheses. A comparison (*t*-test or chi-square) with control group was performed for each test in follow-up examinations. ⁻$P<0.09$; *$P<0.05$; **$P<0.01$; ***$P<0.001$. Insignificant results are with $P>0.1$.
Abbreviations: BNT, Boston Naming Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; IST, Isaacs Set Test; MMSE, mini–mental state examination; NC, normal control; TMT-A, Trail Making Test, part A; TMT-B, Trail Making Test, part B.

The results from language and praxis domains did not reveal significant differences during the period of 1 year.

The patients were classified into three subgroups at baseline: two patients (3%) with NCI, 57 MCI patients (77%), and 15 patients with dementia (20%). At 1 year follow-up investigations, the results revealed 15 NCI patients (20%), 30 MCI patients (41%), and 29 patients with dementia (39%). Eleven patients were lost for follow-up at 12 months.

We followed the patients' subgroups at baseline. The proportion of patients improving or developing dementia and the proportion of patients meeting NCI, MCI, and dementia were determined. From the dementia group, four patients improved their cognitive status – three patients to MCI level and one to NCI – and eight patients remained with dementia. From the MCI patients group, 27 patients remained in MCI, 18 patients became demented, and 12 patients improved to NCI.

Subsequent IST subgroups

The patients were classified into two subgroups according to their IST score at the baseline. IST score of 28 was used as cutoff corresponding to the subjects' educational level.[20] Table 1 presents the distribution of demographic and clinical characteristics according to the IST score subgroups. The number of patients with IST scores (IST >28) within the NL was 46 (44.1%) and those at risk of cognitive decline (IST ≤28) was 39 (45.9%). Furthermore, the patients at risk with IST ≤28 coincided with the same group of patients with IST performance <2.0 SD below the mean from the age-matched control population. Table 3 showed the results of neuropsychological assessments at baseline in patients divided by IST criterion.

Neuropsychological assessments and IST groups

To determine the profile of the follow-up exams on IST and trace the sensitivity of the IST division, a two-way rANOVA on two groups of patients as a between-subject variable and four scores/follow-up exams during 1 year as a within-subject variable was performed. A significant main effect of group factor ($F[1, 72] = 50.84$, $P < 0.001$) and of follow-up exams ($F[3, 216] = 3.61$, $P < 0.05$) was obtained. Main effect of the group showed that patients at risk were having significantly lower IST scores (mean =32) than NL patients (mean =25, Table 4). Most importantly, a significant interaction ($F[3, 216] = 5.85$, $P < 0.001$) was also obtained that suggested different pattern of improvement in IST score over time for both groups (Table 4). In particular, while there was no change in IST over time for NL patients, the patients at risk group showed significant

Table 3 Neuropsychological assessments in patients' subgroups divided by IST criterion

Fifth day	Stroke patients (at risk) IST ≤28	Stroke patients (NL) IST >28
MMSE	25.7 (2.7)	27.3 (1.5)**
• Orientation	9.5 (0.7)	9.8 (0.4)*
• Memory	5.2 (0.9)	5.5 (0.6)*
• Attention	3.8 (1.4)	4.3 (0.8)*
• Language	6.5 (0.7)	6.8 (0.6)*
• Praxis	0.7 (0.4)	0.8 (0.4)
IST	23.5 (4.6)	32.5 (2.7)***
IADL (4 items)	0.31 (0.9)	0.02 (0.1)*
CERAD episodic memory		
– Immediate recall		
• I trial	2.6 (1.4)	3.4 (1.3)**
• II trial	4.4 (1.4)	5.7 (1.6)***
• III trial	5.2 (1.6)	6.6 (1.3)***
– Delayed recall	2.1 (1.9)	4.3 (2.0)***
– Recognition	15.3 (3.0)	17.7 (2.2)***
TMT-A	116 (43)	84 (44)**
TMT-B	248 (62)	176 (66)***
BNT	13.8 (1.2)	14.4 (1.0)*
Figure copying	10.0 (1.2)	10.4 (1.0)
GDS	5.1 (3.4)	3.4 (2.9)*

Notes: Means are given with standard deviations in parentheses separately for patients divided by IST criterion. t-test compares scores between two groups of IST-divided patients. *$P<0.05$; **$P<0.01$; ***$P<0.001$.
Abbreviations: BNT, Boston Naming Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; IST, Isaacs Set Test; MMSE, mini–mental state examination; NL, normal limits; TMT-A, Trail Making Test, part A; TMT-B, Trail Making Test, part B.

improvement in IST score after the 6th month (from 23.5 to 26.7; $P<0.001$); however, significantly lower results of IST scores remained even at 12 months (26.3, Table 4). In the following analyses, two groups based on IST division were taken as a between-subject variable and as a within-subject variable: different neuropsychological measures taken over time. Despite highly significant main effect of patients' subtypes on MMSE scale ($F[1, 72] = 17.17$, $P<0.001$), no main effects of follow-up exams or an interaction were obtained (all $P>0.1$). Thus, MMSE scores did not change over time. Further, IST measure showed significant difference between the patients' groups in memory ($F[1, 72] = 12.21$, $P<0.001$) and delayed response ($F[1, 72] = 15.40$, $P<0.001$); patients at risk always showed worse improvement than NL patients. The interactions were not significant (all $P_s > 0.1$). Word recognition, however, did show dynamic sensitivity to the IST measure. The analysis obtained significant main effects ($F[1, 72] = 20.35$, $P<0.001$; $F[3, 216] = 20.89$, $P<0.001$) and an interaction ($F[3, 216] = 3.42$; KP <0.05). The interaction suggested (Table 4) no improvement in NL patients and a sharp improvement in the patients at risk ($P<0.001$) starting from the second measure in time. Finally, rANOVA on

Table 4 Means of neuropsychological measures ±95% confidence intervals (in parentheses) per condition

IST groups	Measures in time			
	5th day	1st month	6th month	12th month
	IST			
At risk	23.5 (1.5)	25.1 (2.1)	26.7 (1.8)	26.3 (2.1)
NL	32.6 (0.8)	31.4 (1.3)	32.3 (1.5)	31.5 (1.5)
	MMSE			
At risk	25.3 (1.1)	25.7 (0.9)	26.2 (1.0)	25.1 (1.2)
NL	27.1 (0.6)	27.3 (0.4)	27.4 (0.5)	27.3 (0.7)
	Recognition			
At risk	15.3 (1.0)	16.9 (0.8)	17.3 (0.8)	17.3 (0.9)
NL	17.7 (0.7)	18.7 (0.5)	18.6 (0.6)	18.9 (0.4)
	Delayed recall			
At risk	2.1 (0.6)	3.4 (0.8)	3.9 (0.8)	4.1 (0.9)
NL	4.3 (0.6)	5.2 (0.8)	5.3 (0.6)	6.0 (0.7)
	IADL			
At risk	0.3 (0.3)	0.9 (0.4)	0.8 (0.4)	1.4 (0.8)
NL	0.0 (0.0)	0.4 (0.2)	0.3 (0.2)	0.3 (0.2)

Notes: NL group: the patients with IST score within the NL (IST >28). At risk group: those at risk of cognitive decline with IST score ≤28.
Abbreviations: IADL, Instrumental Activities of Daily Living; IST, Isaacs Set Test; MMSE, mini–mental state examination; NL, normal limits.

IADL showed both significant main effects ($F[1, 72] = 11.71$, $P<0.01$; $F[3, 216] = 10.09$, $P<0.001$) and interaction ($F[3, 216] = 4.12$, $P<0.01$). The interaction showed that after 1 year of stroke, patients at risk were less able to take care of themselves ($P<0.001$) than the NL patients (Table 4).

Neuroimaging measures

First, a difference between the two groups in neuroimaging measures was tested. One-way ANOVA was run on the difference between the IST groups and the neuroimaging measures. The results showed that patients at risk have significantly more hippocampal atrophy ($F[1, 83] = 8.32$, $P<0.01$) and basal ganglia lesions ($F[1, 82] = 5.78$, $P<0.05$) than NL patients (Table 5).

Second, simultaneous multiple regressions were carried out with three neuroimaging predictors (PVC, basal ganglia lesions, and hippocampal atrophy on each neuropsychological measure; Table 6). The analyses showed hippocampal atrophy as a very stable predictor of cognitive impairment in almost all measures. Basal ganglia lesions were important only in time and language measures. None of the other predictors contributed to the variance.

Table 5 Means of neuroimaging measures ±95% confidence intervals (in parentheses) per IST group

IST groups	Hippocampal atrophy	Basal ganglia lesions	PVC
At risk	1.2 (0.4)	8.8 (1.7)	2.8 (0.4)
NL	0.6 (0.2)	6.4 (1.2)	2.3 (0.4)

Notes: NL group: the patients with IST score within the NL (IST >28). At risk group: those at risk of cognitive decline with IST score ≤28.
Abbreviations: IST, Isaacs Set Test; NL, normal limits; PVC, periventricular change.

Predictive value of baseline cognitive assessment for subsequent dementia

We compared baseline neuropsychological performances and neuroimaging markers in three patient subgroups (NCI, MCI, and dementia) at 12th month. The results revealed that there were significant differences in hippocampal atrophy ($P<0.05/P<0.0001$), IST ($P<0.01/P<0.01$), TMT-A ($P<0.01/P<0.001$), TMT-B ($P<0.001/P<0.001$), delayed recall ($P<0.001/P<0.001$), recognition ($P<0.001/P<0.01$), immediate recall ($P<0.001/P<0.01$), memory subscale of MMSE ($P<0.01/P<0.01$), and MMSE ($P<0.001/P<0.01$) between the dementia group and the other groups (MCI/NCI) at 1 year follow-up.

Discussion

The objective of our study was to evaluate the delayed changes in cognition in poststroke patients and their relationship to the neuropsychological and neuroimaging markers measured during the acute poststroke phase in first-ever stroke patients. The results of this study revealed that dementia affected up to 20% of patients at the acute phase of stroke and 39% of stroke survivors after 1 year. The frequency of dementia and cognitive impairment after cerebrovascular stroke varies between studies. Ballard et al[3] found that 9% of patients developed incident dementia over the 1-year follow-up period. Madureira et al[21] found the frequency of PSD 3 months after stroke to be only 6%. However, Khedr et al[4] revealed that dementia affects up to 21% of stroke survivors 3 months after stroke. In a subsequent hospitalized cohort studied 3 months after stroke, PSD was found in 26% (66/251).[22] Jonkman et al[23] reported that the incidence of cognitive impairment 3 months after stroke

Table 6 Simultaneous multiple regression analyses on neuropsychological measures (12th month) with neuroimaging predictors

Neuropsychological measures at 12th month	Hippocampal atrophy			Basal ganglia lesions			PVCs		
	β	t	P-value	β	t	P-value	β	t	P-value
MMSE	−0.3	−2.2	0.03	−0.2	−1.9	0.07	0.0	0.1	0.94
MMSE (orientation)	−0.2	−1.6	0.1	−0.2	−1.3	0.2	−0.0	−0.3	0.8
MMSE (attention)	−0.3	−2.4	0.01	−0.1	−1.2	0.2	−0.0	−0.0	0.9
MMSE (memory)	−0.3	−2.4	0.02	−0.1	−0.5	0.6	0.1	0.8	0.4
MMSE (language)	0.1	1.1	0.3	−0.3	−2.4	0.02	−0.1	−0.8	0.4
MMSE (praxis)	−0.1	−1.0	0.3	−0.1	−0.6	0.6	0.1	0.7	0.5
IST	−0.4	−3.3	0.001	−0.2	−1.3	0.19	−0.1	−1.0	0.31
IADL	0.3	2.5	0.01	0.0	0.2	0.83	−0.1	−0.4	0.7
Delayed recall	−0.4	−3.8	0.00	0.0	0.3	0.7	−0.1	0.4	0.7
Recognition	−0.3	−2.9	0.005	−0.0	−0.3	0.7	−0.2	−1.2	0.2
TMT-B	0.3	2.7	0.008	0.3	2.5	0.01	0.2	1.6	0.1
TMT-A	0.3	2.8	0.007	0.3	2.7	0.01	0.1	1.1	0.3

Note: For each predictor, the β, t statistic, and P-value are reported.
Abbreviations: β, beta weight; IADL, Instrumental Activities of Daily Living; IST, Isaacs Set Test; MMSE, mini–mental state examination; PVCs, periventricular changes; TMT-A, Trail Making Test, part A; TMT-B, Trail Making Test, part B.

was 35%–37%. In community-based studies, the prevalence of PSD is approximately 30% and the incidence of new-onset dementia after stroke increases from 7% after 1 year to 48% after 25 years.[6] Our finding falls between these extreme values. Béjot et al[24] examined 3,948 first-ever stroke patients over 24 years. The presence of dementia during the 1st month after stroke was diagnosed in 20.4% of patients. They showed that the prevalence of PSD associated with lacunar stroke was seven times higher than that in intracerebral hemorrhage but declined over time as did prestroke antihypertensive medication. The difference of prevalence of PSD among various studies depends on the study design and the population studied, the criteria used for the diagnosis, neuroimaging markers, vascular risk factors, the time interval between the stroke and the neuropsychological assessment, and length of follow-up.[2,20,22–27]

Although in our study 36.4% of patients had mild depression, this was not significantly associated with poststroke cognitive impairment. In general, depression is a common consequence of stroke with a reported frequency of up to 65% of all patients.[4]

While the prototypic cognitive changes preceding dementia of the Alzheimer type consist of impaired episodic memory, vascular dementia is frequently associated with executive dysfunction. However, many patients are impaired in several cognitive domains, probably reflecting the site and extent of anatomical lesions.[8] In our study, attention, executive functions, processing speed, memory, and orientation were significantly involved in poststroke cognitive impairment. In agreement with our data, a prospective population-based study[28] showed that executive dysfunction as evidenced by verbal fluency and TMT-B performance was significantly associated with early IADL deficits and subsequent

dementia. In addition, Oksala et al[29] showed that in patients with ischemic stroke, cognitive impairment, particularly in executive functions and visuospatial/constructional abilities, is related to poor survival. It should be noted, however, that it is still unclear whether and to what extent deficits in specific cognitive domains predict delayed cognitive and functional decline in patients with ischemic stroke. Identifying poststroke cognitive impairment at an early stage might increase the possibility of reducing or even preventing further cognitive decline. Moreover, an early diagnosis of specific cognitive deficits, such as memory impairment or executive dysfunction, could be of great importance in determining the effect on daily functioning.[7,30]

The results of the present study revealed that neurological and daily living activity outcome 1 year after stroke in cognitively intact patients is significantly higher than in patients at risk measured by IST at baseline. We found that IST as a screening test could be a reliable and quick tool for poststroke cognitive impairment evaluation and delayed cognitive and neurological outcome. Our results, however, showed that MMSE did not appear to be a significant predictor. Although the MMSE is one of the most frequently used cognitive tests in research and clinical practice, Al-Qazzaz et al[31] and Nys et al[32] found that the MMSE is an invalid screening tool for discriminating between cognitively intact and impaired stroke patients. In agreement with this finding, a study focusing on young (18–47 years old) stroke patients also suggested that the MMSE is not able to detect a neuropsychological deficit.[33] Thus, studies confirm that MMSE is not always an effective tool of measuring neuropsychological deficits.

It should be noted that there is evidence suggesting that assessing additional cognitive functions, such as executive

functioning, abstract reasoning, and speed of information processing, might improve the screening, because impairments in these areas are often significant predictors of both cognitive and functional impairment over the long term. However, extensive neuropsychological testing is time consuming and can be exhausting for the patient. Thus, short appropriate cognitive screening seems to be the obvious best way to detect cognitive impairments in the early days poststroke.[7] The Tel Aviv Brain Acute Stroke Cohort (TABASCO) study is an ongoing, prospective cohort study that plan to recruit approximately 1,125 consecutive first-ever mild to moderate stroke patients. Using a computerized battery of neuropsychological tests for memory, attention, and executive functions (MindStreams®) in 545 poststroke patients demonstrated that either of the modalities alone is sensitive enough for identifying subtle cognitive impairment.[34]

The role of neuroimaging markers including PVCs and MTLA as a contributor to poststroke cognitive decline is still controversial.[8] In our study, hippocampal atrophy assessed by visual scale is the strongest predictor of cognitive impairment and dementia outcome, even in poststroke patients. Poststroke patients at risk of cognitive impairment showed significantly more basal ganglia lesions in comparison with cognitively intact stroke patients. Although CT is less accurate than MRI in demonstrating the degree of PVCs, a previous study showed a good agreement between grading of changes on these scales on CT and MRI.[13]

PSD is well documented in patients with extensive subcortical white matter lesions.[24] However, 30% of normal individuals over 65 years of age have moderate white matter hyperintensities (WMH) on MRI and 7% have severe WMH.[8,35] Stebbins et al demonstrated significant gray matter volume reductions, mostly in thalamus in patients with stroke with one or more cognitive domain impairments compared with patients with stroke without cognitive impairment using voxel-based optimized morphometry techniques.[36] A recent study showed that in the whole stroke group, putamen lacunes were correlated with impairment in memory, while WMH and hippocampal volume both correlated with global dysfunction.[37] Another study found that delayed PSD in elderly stroke survivors is associated with MTLA.[38] Hénon et al[27] showed that patients who had a stroke and MTLA more frequently develop dementia than patients without MTLA, but their study does not suggest that MTLA independently contributes to dementia. Firbank et al[39] found that medial temporal atrophy rather than WMH predict cognitive decline in stroke survivors, suggesting a greater role for Alzheimer's type than vascular pathology in delayed cognitive impairment after stroke. In contrast, recent studies revealed that midlife vascular risk factors are associated with an increased rate of global and hippocampal atrophy. Moreover, hippocampal atrophy is presented not only in Alzheimer's disease but also in cerebrovascular disease and subcortical vascular dementia. These data could explain cognitive deficits related to hippocampal atrophy in a pure vascular process.[40,41]

Strengths of our study included the prospective and consecutive recruitment of a well-characterized cohort of Bulgarian stroke patients and controls. The patients were thoroughly examined four times with neuropsychological sensitive battery for a period of 1 year.

The main limitations of the current study might be our small sample size for detecting longitudinal decline and use of CT instead of MRI for assessing the neuroradiological markers. However, there is evidence of excellent intraobserver agreement between CT and MRI for medial temporal atrophy and WMC with published visual rating scales.[13]

Conclusion

Executive functioning deficit appears to have a predictive power for cognitive impairment progression. IST as a screening test has the potential to be a reliable and quick tool for poststroke cognitive impairment evaluation and delayed cognitive and neurological outcome. Hippocampal atrophy is the strongest predictor for cognitive impairment outcome, even in poststroke cognitive impairment. Identifying the neuropsychological and neuroimaging markers for delayed cognitive and functional decline may set the stage for better poststroke management and lead to important therapeutic implications.

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Disclosure

The authors report no conflicts of interest in this work.

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