Depressive Symptoms Following Stroke and Transient Ischemic Attack:

Is It Time for a More Intensive Treatment Approach? Results From the TABASCO Cohort Study

Oren Tene, MD[a,b]; Shani Shenhar-Tsarfaty, PhD[a]; Amos D. Korczyn, MD[b]; Efrat Kliper, PhD[a,b]; Hen Hallevi, MD[a,b]; Ludmila Shopin, MD[a]; Eitan Auriel, MD[a]; Anat Mike, MA[a]; Natan M. Bornstein, MD[a,b,*]; and Einor Ben Assayag, PhD[a]

ABSTRACT

Objective: To examine whether depressive symptoms after a stroke or a transient ischemic attack (TIA) increase the risk of cognitive impairment and functional deterioration at 2-year follow-up.

Methods: Participants were survivors of first-ever, mild-to-moderate ischemic stroke or TIA from the TABASCO prospective cohort study who underwent 3T magnetic resonance imaging and were examined by a multiprofessional team 6, 12, and 24 months after the event using direct interviews, depression scales, and neurologic, neuropsychological, and functional evaluations. The main outcome was the development of cognitive impairment, either mild cognitive impairment (MCI) or dementia. MCI was diagnosed by a decline on at least 1 cognitive domain (≥ 1.5 SD) of the Montreal Cognitive Assessment score and/or on the computerized neuropsychological battery, as compared with age- and education-matched published norms. Dementia was diagnosed by a consensus forum that included senior neurologists specializing in memory disorders and a neuropsychologist.

Results: Data were obtained from 306 consecutive eligible patients (mean age: 67.1 ± 10.0 years) who were admitted to the department of emergency medicine at the Tel Aviv Medical Center from April 1, 2008, to December 1, 2011, within 72 hours from onset of symptoms of TIA or stroke. Of these patients, 51 (16.7%) developed cognitive impairment during a 2-year follow-up. Multivariate regression analysis showed that a Geriatric Depression Scale (GDS) score ≥ 6 at admission and at 6 months after the event was a significant independent marker of cognitive impairment 2 years after the stroke/TIA (OR = 3.62, 95% CI, 1.01–13.00; OR = 3.68, 95% CI, 1.03–13.21, respectively). A higher GDS score at 6 months was also related to a worse functional outcome ($P < .001$).

Conclusions: Our results support depression screening among stroke and TIA survivors as a tool to identify patients who are prone to have a worse cognitive and functional outcome. These patients may benefit from closer medical surveillance and a more intensive treatment approach.

Trial Registration: ClinicalTrials.gov identifier: NCT01926691

J Clin Psychiatry 2016;77(5):673–680
dx.doi.org/10.4088/JCP.14m09759

[a]Departments of Neurology and Psychiatry, Tel Aviv Medical Center, Tel Aviv, Israel
[b]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
*Corresponding author: Natan M. Bornstein, MD, Department of Neurology, Tel-Aviv Sourasky Medical Center, 6 Weizmann St, Tel Aviv 64239, Israel (natanb@tlvmc.gov.il).

The association between depression and a variety of cognitive disorders in the elderly—from mild cognitive impairment (MCI)[1,2] to full blown dementia[3–5]—is well established.

The term *poststroke dementia* is used to define any dementia occurring after a stroke irrespective of the cause. Poststroke dementia is a frequent condition, and its prevalence ranges from 6% to 32% of stroke survivors.[6] Depression is the most frequent noncognitive neuropsychiatric complication of brain ischemia, affecting up to a third of all such patients.[7,8] Poststroke depression is associated with increased mortality,[9] higher disability and anxiety levels, and lower quality of life.[10,11] Despite its great clinical relevance, the relationship between stroke, depression, and dementia remains relatively unexplained.

We examined whether depressive symptoms (not necessarily a major depressive disorder) identified within 72 hours after admission to the hospital due to a mild-to-moderate first-ever ischemic stroke or transient ischemic attack (TIA) are associated with a worse cognitive and functional status at a 2-year follow-up. Since controversy exists regarding the appropriateness of diagnosing depression in the setting of an acute stroke, we examined Geriatric Depression Scale (GDS) results 6 months after the index event as well.

METHODS

Study Population

Participants were consecutive eligible patients in the Tel Aviv Brain Acute Stroke Cohort (TABASCO) study.[12] Patients included were men and women over 50 years of age, admitted within 72 hours after an acute stroke/TIA, with a total score on the NIH Stroke Scale[13] (NIHSS) < 17. Exclusion criteria were hemorrhagic stroke, cognitive impairment before the stroke (determined by Informant Questionnaire on Cognitive Decline in the Elderly[14] score ≥ 3.3), and severe aphasia or disability that made unlikely the possibility of continuous follow-up. All participants signed informed consent forms, approved by the local ethics committee. The study was registered at ClinicalTrials.gov (identifier: NCT01926691).

Depressive Symptoms

Depressive symptoms were assessed within 72 hours of admission and again 6, 12, and 24 months later using the

15-item GDS.[15] A score ≥ 6 may indicate a depressive episode.[15] The 15-item GDS has been shown to have acceptable internal consistency and reliability (ie, Cronbach α ≥ 0.70) in older adults from a range of populations.[16]

Baseline and Follow-Up Cognitive Assessments

Patients completed a baseline neuropsychological assessment including the Montreal Cognitive Assessment (MoCA)[17] and NeuroTrax computerized cognitive testing (Mindstreams, NeuroTrax Corp, Bellaire, Texas).[18] These comprehensive neuropsychological evaluations were repeated 6, 12, and 24 months after the event. A global cognitive score was computed as the average of the 6 index scores (memory, executive functioning, visuospatial perception, verbal functioning, attention, and motor skills). Data for each outcome parameter were normalized according to stratifications of age (50–70 years, > 70 years) and education (≤ 12 years, > 12 years) to give a distribution with a mean of 100 and a standard deviation of 15 (ie, an IQ-style scale).

Criteria for Cognitive Impairment

Patients with cognitive impairment were diagnosed as having either MCI or dementia.

To diagnose MCI, the modified Petersen criteria[19] were applied: the subject had to be impaired (≥ 1.5 SD) on at least 1 cognitive domain compared with age- and education-matched published norms on the MoCA score,[20,21] have no impairment of basic functional activities, and not fulfill the *DSM-IV-TR* criteria for dementia. The norms for the NeuroTrax computerized cognitive testing were previously published.[22,23]

Participants with suspected cognitive impairment were referred to a senior clinician (A.D.K.) for assessment. Included were patients who could not complete the MoCA or whose NeuroTrax test had decreased by ≥ 1.5 SD in the follow-up examinations, those who had cognitive complaints, and those who were suspected by a senior neurologist of having cognitive impairment.

Assessments were further reviewed by a consensus forum to determine whether the participant had dementia or MCI. The forum included the assessor, 3 senior neurologists specializing in memory disorders, and a neuropsychologist.

Functional Assessments

Participation in real-world activities and instrumental activities of daily living (ADL) measures were assessed using the ADL/instrumental ADL domain in the Stroke Impact Scale (SIS). The SIS version 3 is a comprehensive measure of health-related quality of life in stroke populations, with established reliability and validity.[24]

Patients' rehabilitation and return to normal function were assessed using the Reintegration to Normal Living Index (RNL). In previous studies, the internal consistency of the RNL ranged from α = 0.80 to 0.90; test-retest reliability was $r = 0.83$ in subjects over 75 years old.[25]

Clinical Points

- Cognitive impairment is a frequent and serious outcome of stroke and transient ischemic attack (TIA), but the relationship between them is relatively unexplained, and there are few accepted indicators to identify patients at high risk of developing poststroke dementia.
- If patients present with a stroke or TIA and develop depressive symptoms immediately after the index event, or 6 months later, as measured by a simple questionnaire such as the Geriatric Depression Scale, they have a higher chance of developing cognitive decline and probably warrant a more aggressive treatment approach.

MRI Analyses of the Participants

MRI images were acquired within 7 days of stroke onset on a 3T GE scanner (GE Signa EXCITE, Milwaukee, Wisconsin) using an 8-channel head coil. Presence of an acute ischemic infarct was assessed by a senior neuroradiologist, based on the diffusion weighted imaging. Volumes (in mm^3) of ischemic lesions were calculated. The quantification of the ischemic lesions was performed using a semiautomatic method[26] without knowledge of the clinical data.

White matter hyperintensities, the imaging counterparts of white matter lesions, were identified on FLAIR scans and rated semiquantitatively based on a 4-point scale according to the Fazekas-Wahlund periventricular score.[27]

Statistical Analysis

To examine the associations between depressive symptoms and risk for cognitive impairment over the 2-year follow-up, Cox proportional regression analyses were used to obtain univariate proportional hazard ratios with time (months) from index stroke to cognitive impairment as the dependent variable. Significant predictors of cognitive impairment were entered into a multivariate forward stepwise Cox regression model ($P < .05$ for entry, $P > .1$ for removal).

Comparisons or distributions between categories were assessed using the Student t test, Mann-Whitney U or χ^2 test, as appropriate. Associations between numeric variables were determined using the Pearson or Spearman rank correlation analysis (coefficient estimate r). Statistical differences between longitudinal cognitive curves of the different groups were analyzed by a 2-way analysis of variance, using the Bonferroni correction.

For the purpose of data reduction across-domain comparison, raw cognitive test scores were converted to Z scores, with positive values indicating better performance and negative values indicating worse performance.

A P value less than .05 was considered statistically significant for all analyses. SPSS/WIN (version 19.0, SPSS, Chicago, Illinois) software was used for all statistical analyses.

RESULTS

Participants

A total of 472 consecutive eligible patients admitted to the Department of Emergency Medicine at Tel Aviv Medical

Table 1. Baseline Demographic Characteristics and Clinical, Cognitive, and Follow-Up Characteristics of Poststroke Survivors

	All Participants	GDS Score < 6	GDS Score ≥ 6
Demographic characteristics			
N	306	261	45
Age, mean (SD), y	67.1 (10.0)	66.9 (9.9)	68.2 (10.1)
Male gender, n (%)	182 (59.5)	158 (60.5)	24 (53.3)
Education, mean (SD), y	13.2 (3.7)	13.4 (3.7)	11.8 (3.2)*
Body mass index, kg/m^2, mean (SD)	27.2 (4.3)	27.3 (4.4)	26.5 (3.9)
Ethnicity, n (%)			
Ashkenazi	197 (64.4)	170 (65.1)	27 (60.0)
Sephardic	88 (28.8)	73 (27.9)	15 (33.3)
Mixed	21 (6.8)	19 (7.3)	2 (4.4)
Not performed MRI, n (%)	55 (18.0)	41 (15.7)	14 (31.1)
White matter lesion score, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)
Vascular risk factors or medical history, n (%)			
Current smokers	74 (24.2)	61 (23.4)	13 (28.9)
Diabetes mellitus	28 (9.2)	27 (10.3)	2 (4.4)
Dyslipidemia	159 (52.0)	136 (52.1)	23 (51.1)
Hypertension	182 (59.5)	155 (59.4)	27 (60.0)
Ischemic heart disease	55 (18.0)	41 (15.7)	14 (31.1)*
Myocardial infarction	28 (9.2)	22 (8.4)	6 (13.3)
No. of cardiovascular risk factors, median (IQR)	1 (1–2)	1 (1–2)	1.5 (1–2)
Married (or living with spouse), n (%)	210 (68.6)	181 (69.3)	29 (64.4)
*APOE** ε4 allele, n (%)	50 (16.3)	44 (16.9)	6 (13.3)
Working, n (%)	165 (53.3)	142 (57.3)	21 (36.2)*
Religious, n (%)	22 (7.2)	20 (7.7)	2 (4.4)
Regular physical activity, n (%)	139 (45.4)	130 (49.8)	9 (20.0)**
Physical activity, min/wk, mean (SD)	208.8 (163.3)	209.3 (153.9)	204.9 (235.0)
Clinical, cognitive, and follow-up characteristics			
Admission NIHSS, median (IQR)	2 (0–4)	2 (0–4)	2 (1–4)
Lesion location			
New lesion in MRI, n (%)	167 (66.5)	150 (68.2)	17 (54.8)
Supratentorial stroke, n (%)	146 (87.4)	131 (87.3)	15 (88.2)
Left (%)	60 (41.1)	71 (54.2)	6 (40.0)
Right (%)	60 (41.1)	54 (41.2)	9 (60.0)
Bilateral (%)	6 (4.1)	6 (4.6)	0
Infratentorial stroke, n (%)	21 (12.6)	19 (12.7)	2 (11.8)
Infarct volume, mm^3 (TIA patients included), median (IQR)	212 (0–860)	1,392.0 (628.0–3,752.0)	0 (0–3,648.0)
Assessments at admission			
Computerized global cognitive score, mean (SD)	91.8 (14.1)	91.9 (14.6)	91.3 (9.3)
MoCA score, mean (SD)	23.8 (3.3)	23.8 (3.4)	23.5 (3.2)
Geriatric Depression Scale score, median (IQR)	2 (1–4)	2 (0–3)	7 (6–10)**
Assessments 6 months poststroke/TIA			
Modified Rankin Scale[29]			
Score, median (IQR)	0 (0–1)	0 (0–1)	1 (0–1)
Good outcome (score 0–1), n (%)	254 (83.0)	213 (81.6)	39 (86.7)
Computerized global cognitive score, mean (SD)	94.1 (12.5)	94.8 (12.1)	89.4 (14.1)*
MoCA score, mean (SD)	25.0 (3.7)	25.1 (3.5)	24.2 (4.6)
SIS-ADL score, median (IQR)	50 (48–50)	50 (49–50)	47 (42–50)*

*P < .05.
**P < .005, respectively, between the GDS < 6 and the GDS ≥ 6 groups.
Abbreviations: IQR = interquartile range, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation, SIS-ADL = Stroke Impact Scale—activities of daily living, TIA = transient ischemic attack.

Center from April 1, 2008, to December 1, 2011, within 72 hours from onset of symptoms of TIA or stroke were included. Individuals whose GDS results or cognitive data were missing or who were deceased before follow-up were excluded (123). Also excluded were patients who reported having had depression in the past (43). Thus, a total of 306 patients remained for analysis. These participants had a mean age of 67.1 (± 10.0) years; 59.5% were male; and 79 (25.8%) were diagnosed as suffering from TIA.

The stroke etiologies (based on TOAST criteria[28]) were as follows: 135 lacunar stroke (59.5%), 33 cardioembolic stroke (14.5%), 17 large-artery atherosclerotic stroke (7.5%), 42 stroke of other or undetermined etiology (18.5%). No differences in baseline GDS scores were observed between stroke subtypes or between stroke and TIA patients, and they were therefore grouped together for further analyses.

A summary of baseline characteristics of the participants is shown in Table 1. Included patients did not significantly differ on demographical and clinical characteristics from those who were excluded.

Prevalence and Incidence of Depressive Symptoms and Cognitive Impairment

Immediately after the stroke/TIA, 45 patients (14.7%) had a GDS score ≥ 6 (higher baseline GDS group), while 6 months later, 58 patients (19%) had a GDS score ≥ 6 (higher 6 months GDS group). Of the higher baseline GDS group, 26 patients (57.8%) retained their depressive symptoms 6 months later or even had a worsening of their symptoms. Those whose depressive symptoms worsened did not differ on any parameter from those whose symptoms improved. From the entire cohort, 76 (24.8%) retained the same GDS score, 130 (42.5%) had worsening of their symptoms, and 100 (32.7%) had improvement of their symptoms. Those whose depressive symptoms worsened were less educated than those who retained the same score or improved (12.3 ± 3.5 vs 13.8 ± 3.8 education years, P = .001) and were more likely to have a lesion in the right hemisphere (35.8% vs 21.7%, P = .013).

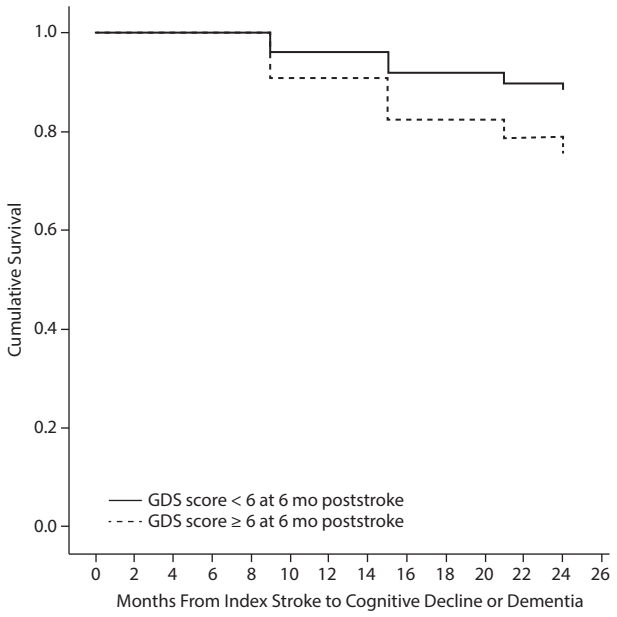
A higher baseline GDS score was associated with lower education, history of ischemic heart disease, lower physical activity, and unemployment (P = .01, P = .013, P < .001, P = .053, respectively). A higher GDS score at 6 months was associated with female gender and smoking, as well as the above characteristics (P = .054, P = .048, P = .001, P = .005, P = .011, P = .004, respectively). The higher GDS groups at both time points had larger infarct volume at hospital admission, but this was insignificant due to wide variance (Table 1). There was no significant difference in use

Table 2. Univariate and Multivariate Predictors of Cognitive Impairment Within 24 Months From Stroke

Baseline Characteristic	Cognitive Decline Relative Hazard Ratio (95% CI)[a]
Univariate predictors	
Age ≥ 75 y	**5.09 (2.61–9.93)**
Male gender	1.14 (0.62–2.09)
Education < 12 y	**2.53 (1.31–4.89)**
Ethnicity, Ashkenazi	1.68 (0.88–3.22)
Ethnicity, Sephardic	1.02 (0.28–3.69)
Married (or living with spouse)	1.58 (0.82–3.01)
Physical activity	1.00 (0.99–1.01)
New lesion in MRI	1.74 (0.78–3.88)
Lesion location	1.01 (0.99–1.01)
Infarct volume	0.67 (0.32–1.40)
Stroke vs TIA	2.00 (0.98–4.08)
Ischemic heart disease	**2.53 (1.28–5.01)**
Hypertension	**2.25 (1.15–4.43)**
Diabetes mellitus	1.41 (0.54–3.66)
Dyslipidemia	1.40 (0.76–2.57)
Ever smoked	0.82 (0.38–1.74)
Recurrent strokes	0.83 (0.10–7.05)
APOE ε4 allele	1.59 (0.75–3.37)
White matter lesion score	**1.55 (1.06–2.28)**
NIHSS at hospital admission	1.10 (0.99–1.22)
MoCA score at hospital admission	**0.75 (0.66–0.84)**
MoCA score at 6 mo poststroke	**0.76 (0.69–0.84)**
Computerized global cognitive score at hospital admission	**0.95 (0.92–0.98)**
Computerized global cognitive score 6 mo poststroke	**0.93 (0.90–0.96)**
GDS score at hospital admission ≥ 6	**2.38 (1.15–4.95)**
GDS score 6 mo poststroke ≥ 6	**2.61 (1.33–5.11)**
Antidepressant treatment 6 mo poststroke	1.88 (0.79–4.47)
Multivariate predictors—model 1	
MoCA score at hospital admission	**0.77 (0.65–0.91)**
Age ≥ 75 y	**4.49 (1.43–14.14)**
Admission GDS score ≥ 6	**3.62 (1.01–13.00)**
Multivariate predictors—model 2	
MoCA score at hospital admission	**0.79 (0.67–0.93)**
Age ≥ 75 y	**4.16 (1.14–15.26)**
GDS score 6 mo poststroke ≥ 6	**3.68 (1.03–13.21)**

[a]Significant results are shown in bold ($P < .05$).
Abbreviations: CI = confidence interval, GDS = Geriatric Depression Scale, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, NIHSS = National Institutes of Health Stroke Scale, TIA = transient ischemic attack.

Figure 1. Survival Curves Showing Time to Cognitive Impairment by GDS Score at 6 Months Poststroke



Abbreviation: GDS = Geriatric Depression Scale.

of antidepressants 6 months poststroke between the groups with higher and lower GDS scores at 6 months (13.8% vs 9.3%, $P = .305$).

Patients in the higher baseline GDS group showed significantly inferior cognitive results at 6 and 24 months after the index event compared to patients in the lower baseline GDS group, but not at 12 months ($P = .019$, $P = .002$ at 6 and 24 months, respectively, $P = .098$ at 12 months). Patients who had higher GDS scores at 6 months showed significant inferior cognitive results at all time points (6, 12, and 24 months: $P < .001$, $P = .001$, $P < .001$, respectively), although their cognitive results did not differ from those of patients in the lower GDS group at hospital admission ($P = .414$).

During the follow-up period of 2 years poststroke, 51 participants (16.7%) developed clinically significant cognitive impairment, as defined in Methods. Of these, 8 patients (2.6%) developed dementia and 43 patients (14.1%) developed MCI. Two patients were diagnosed as having MCI within 6 months from their acute event and were therefore excluded from the univariate as well as the multivariate analyses exploring the contribution of depressive symptoms at 6 months poststroke/TIA. No significant differences in GDS scores were observed retrospectively between MCI or dementia patients, and they were therefore grouped together as a "cognitive impairment group."

Univariate and Multivariate Predictors of Cognitive Impairment

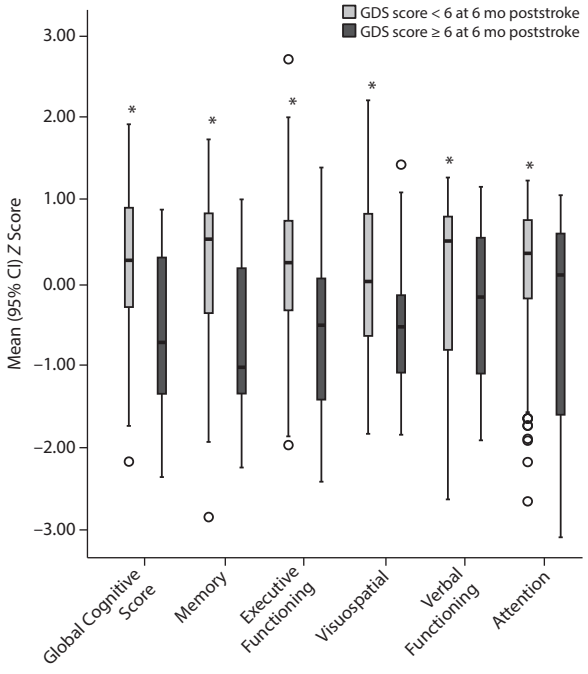
Univariate and multivariate predictors of cognitive impairment during the 2-year follow-up period are shown in Table 2. Univariate predictors included age, lower education (< 12 years), ischemic heart disease, hypertension, white matter lesion score, and cognitive and GDS scores at admission and 6 months later.

Stroke severity, as measured by NIHSS scoring at hospital admission, lesion location, or infarct volume, did not emerge as significant predictors of cognitive impairment in this cohort.

In multivariate analysis predicting time to cognitive impairment, predictors retained were baseline cognitive scores, age ≥ 75 years, and GDS score ≥ 6 at either hospital admission (model 1) or 6 months later (model 2). Figure 1 shows the survival curve to cognitive impairment according to GDS score 6 months poststroke/TIA.

Model 1 correctly predicts 88.3% of the cases, while model 2 correctly predicts 89.0% of the cases. We chose to focus on model 2, as we assumed that the baseline GDS, performed in the acute hospital setting, might be more vulnerable to false-positive results.

Figure 2. Cognitive Performance 2 Years After Stroke/TIA by GDS Score at 6 Months Poststroke[a]



[a]Small circles indicate unusual cases/values to the *Z* score.
*Significant difference between groups ($P < .05$).
Abbreviations: GDS = Geriatric Depression Scale, TIA = transient ischemic attack.

Association Between GDS Scores at Admission and 6 Months and Performance on Specific Cognitive Domains

Patients in the group with higher GDS scores at admission had worse cognitive performance on most of the cognitive domains tested at a 2-year follow-up and received a lower global cognitive score compared with the lower GDS score group (global cognitive score: $P = .002$, memory: $P = .005$, executive functioning: $P = .005$, visuospatial: $P = .003$, verbal functioning: $P = .474$, attention: $P = .074$). Patients in the group with higher GDS scores at 6 months had worse cognitive performance on all 5 cognitive domains tested at a 2-year follow-up (global cognitive score: $P < .001$, memory: $P < .001$, executive functioning: $P < .001$, visuospatial: $P = .001$, verbal functioning: $P = .054$, attention: $P = .017$; Figure 2).

Longitudinal Changes in GDS Score, Cognitive Function, Activities of Daily Living, and Reintegration to Normal Living

GDS. On average, GDS scores in the group with higher GDS scores at baseline remained high at 6, 12, and 24 months poststroke ($P < .001$ for all time points). The same was true for the group with higher GDS score at 6 months (Figure 3A).

Cognitive function. Overall, most patients' cognitive function improved from baseline to 6 months (72.5%) and from 6 to 12 months poststroke (64.8%) ($P < .001$ for both measures), but only the groups with lower GDS scores at baseline or 6 months retained the improvement at 12 to 24 months (Figure 3B; < 6 and ≥ 6 GDS score groups in Figure 3 are scores from 6 months poststroke).

Post hoc tests revealed that the groups with lower and higher GDS scores at 6 months differed significantly in cognitive scores 12 and 24 months poststroke ($P = .002$ for the difference between curves).

Activities of daily living. Patients in the group with higher GDS scores at baseline presented significantly lower levels of ADL function at 6 months, but not at 12 or 24 months, compared to the lower GDS group ($P = .21$, $P = .401$, $P = .441$, respectively), while the group with higher GDS scores at 6 months showed significantly lower levels of ADL function at all time points compared to the lower GDS group ($P < .001$, $P = .003$, $P < .001$ for 6, 12, and 24 months, respectively; Figure 3C).

Reintegration to Normal Living Index. Patients in the group with higher GDS scores at baseline showed significantly reduced RNL measures at 6 and 12 months, but not at 24 months, compared to the lower GDS group ($P = .004$, $P = .003$, $P = .067$, respectively), while the group with higher GDS scores at 6 months had significantly reduced RNL measures at all time points compared to the lower GDS group ($P < .001$ for all time points; Figure 3D).

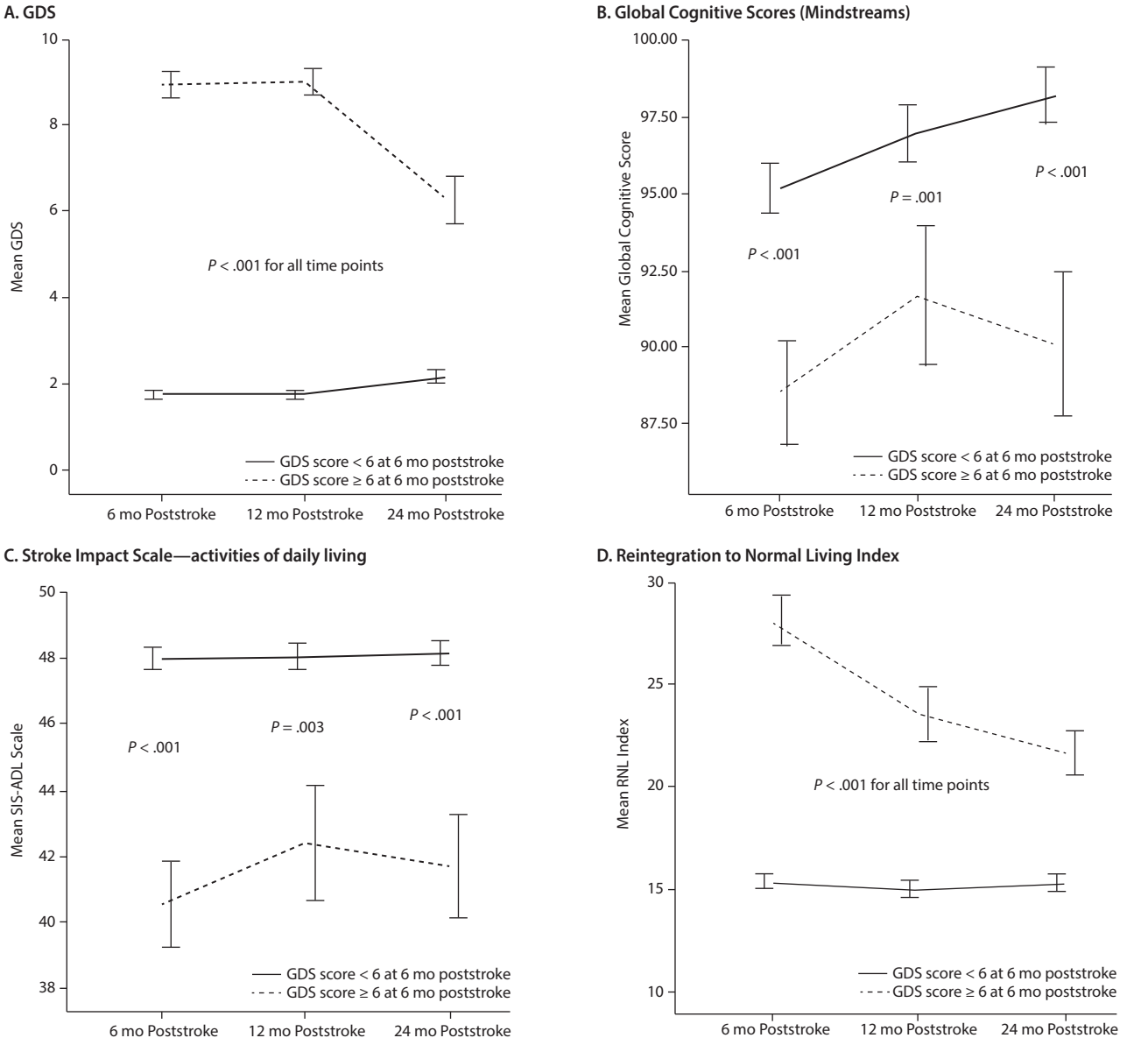
CONCLUSIONS

We report that depressive symptoms in poststroke/TIA patients are associated with cognitive impairment (either dementia or MCI) and functional deterioration at 2-year follow-up. This association is observed immediately after the stroke/TIA and becomes more significant 6 months after the index event (Figure 3). Our study excluded patients with a history of depression and/or cognitive decline, and although it is impossible to rule out that subtle and undiagnosed neurodegenerative changes commenced prior to the stroke, the overt cognitive deterioration of patients occurred after the ischemic brain insult.

We found that only 16.7% of our participants developed cognitive impairment. This prevalence is possibly lower than expected, potentially because our study excluded patients with severe stroke and because most participants were relatively well educated. Importantly, it is not necessarily a major depressive episode (according to *DSM-IV-TR* criteria) that predicts the worse outcome seen in the higher GDS groups, but merely the existence of (at times, few) depressive symptoms. Patients with a score of 6 or higher on the GDS might not even feel depressed, nor develop the main features of a full blown depressive episode.

The relationship between stroke, depressive symptoms, and cognitive impairment is complex, and the mechanisms underlying these processes remain largely unknown. Allan et al,[30] after studying older (> 75 years) poststroke patients, found that baseline depression was a predictor of death, and possibly dementia, but concluded that the interaction between depression and dementia requires further investigation.

Figure 3. Longitudinal Changes in GDS Score, Cognitive Function, Reintegration to Normal Living, and Activities of Daily Living by GDS Score at 6 Months Poststroke



Abbreviation: GDS = Geriatric Depression Scale.

Parikh and colleagues[31] reported that poststroke patients with an in-hospital diagnosis of depression (major or minor) were significantly more impaired in physical activities and language functioning on a 2-year follow-up. Willey et al[32] found that stroke patients who reported depressed mood within the week following their stroke were more likely to be severely disabled 24 months after the stroke. Kauhanen et al[33] found that poststroke depression correlates with cognitive impairment a year after a stroke. His team studied a smaller group (106 patients) with a more severe stroke.

Many studies have evaluated the cognitive outcome of depression, but not necessarily after stroke/TIA. These studies regularly describe a strong association between depression and cognitive impairment.[34] Even subsyndromal depressive symptoms are considered as a risk factor for the development of cognitive impairment.[35]

Our study does not aim to determine whether depression is a consequence of stroke, or if dementia results from poststroke depression. Rather, we suggest that a group of patients who survived brain ischemia, but developed depressive symptoms, do worse compared to their nondepressed counterparts in recovering from their brain insult. They perform worse in all cognitive tests and have greater difficulties in returning to normal life. It is possible that a common mechanism with similar risk factors influences the brain and leads to this cluster of symptoms—such as hyperactivity of the hypothalamic-pituitary-adrenal axis, silent brain infarcts, or the presence of

chronic brain inflammation.[36–38] Currently, we are studying the mechanisms underlying the findings described, but even at this point it is prudent to suggest using the GDS, or any other simple screening tool that assesses depressive symptoms after stroke, to identify high-risk patients who may benefit from an intensive treatment approach. More studies are still needed to determine the exact therapeutic interventions and their targets, either behavioral adaptations and stroke rehabilitation interventions[39] and/or the use of antidepressants, antiinflammatory agents, or better preventative antiplatelet aggregation medication.

The timing in which depressive symptoms were assessed in our study needs to be addressed. We accept the assumption that GDS completed immediately after a stroke/TIA, in the hospital setting, may reflect false-positive results. Therefore, we chose to focus also on GDS results at 6 months after the stroke/TIA. At this time point, the association between depressive symptoms and a worse cognitive and functional outcome was stronger than immediately after the stroke/TIA. In future studies, we suggest evaluating depressive symptoms at a time point more adjacent to the stroke/TIA, but not in the hospital setting (eg, 4 weeks after the index event).

The strengths of our study include a fairly large number of consecutive subjects, the extensive study protocol, the systematic follow-up with careful prospective surveillance of clinical events and cognitive performance, and the use of a consensus forum of specialists for determining cognitive status.

Several limitations of our study need to be addressed. First, we note the inclusion of only patients with mild-to-moderate clinical manifestations, who were expected to be able to perform cognitive tests and be available for follow-up. Nevertheless, establishing a relationship between mild stroke/TIA to depression and cognitive impairment is more challenging than between severe stroke and the above. Second, our follow-up was too short to indicate whether depressive symptoms also predict future deterioration, as we expect, although data seem to support the GDS as a predictive tool for cognitive impairment as early as 12 months after the stroke/TIA. Third, and as stated above, our study does not determine the causality of poststroke cognitive decline, but merely points to the strong association between depressive symptoms after an ischemic brain insult and a future cognitive impairment. Last, we acknowledge the lack of a nonstroke control group.

Enhancing quality of life and improving daily functions are the ultimate goals of stroke rehabilitation. Earlier identification of patients at risk for cognitive, functional, or social deterioration is crucial. In this study, the use of a simple tool, the GDS, helped identify a "poorer outcome" subset of patients after stroke/TIA. These patients usually do not meet criteria for a major depressive episode and are not referred to psychiatric care. Their early identification calls for applying therapeutic interventions and closer medical surveillance, in hope of reversing their unfavorable outcome.

Submitted: December 24, 2014; accepted May 19, 2015.

Online first: March 29, 2016.

Potential conflicts of interest: All authors declare no conflict of interest.

Funding/support: This study is supported by grants 3000000-5062 and 30000-9651 from the Chief Scientist Office, Ministry of Health, Israel, grant RAG11482 from the American Federation for Aging Research, and grant 2011344 From the US-Israel Bi-national Science Foundation.

Role of the sponsor: These funding agencies had no role in the conduct and publication of this study.

REFERENCES

1. Geda YE, Knopman DS, Mrazek DA, et al. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. *Arch Neurol*. 2006;63(3):435–440.
2. Yaffe K, Blackwell T, Gore R, et al. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. *Arch Gen Psychiatry*. 1999;56(5):425–430.
3. Paterniti S, Verdier-Taillefer MH, Dufouil C, et al. Depressive symptoms and cognitive decline in elderly people: longitudinal study. *Br J Psychiatry*. 2002;181(5):406–410.
4. Modrego PJ, Ferrández J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. *Arch Neurol*. 2004;61(8):1290–1293.
5. Keefe RS, McClintock SM, Roth RM, et al. Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review. *J Clin Psychiatry*. 2014;75(8):864–876.
6. Pasi M, Poggesi A, Salvadori E, et al. Post-stroke dementia and cognitive impairment. *Front Neurol Neurosci*. 2012;30:65–69.
7. Catapano F, Galderisi S. Depression and cerebral stroke. *J Clin Psychiatry*. 1990;51(suppl):9–12.
8. Allan LM, Rowan EN, Thomas AJ, et al. Long-term incidence of depression and predictors of depressive symptoms in older stroke survivors. *Br J Psychiatry*. 2013;203(6):453–460.
9. Loubinoux I, Kronenberg G, Endres M, et al. Post-stroke depression: mechanisms, translation and therapy. *J Cell Mol Med*. 2012;16(9):1961–1969.
10. Murray V, von Arbin M, Bartfai A, et al. Double-blind comparison of sertraline and placebo in stroke patients with minor depression and less severe major depression. *J Clin Psychiatry*. 2005;66(6):708–716.
11. Ayerbe L, Ayis S, Crichton S, et al. The long-term outcomes of depression up to 10 years after stroke; the South London Stroke Register. *J Neurol Neurosurg Psychiatry*. 2014;85(5):514–521.
12. Ben Assayag E, Korczyn AD, Giladi N, et al. Predictors for poststroke outcomes: the Tel Aviv Brain Acute Stroke Cohort (TABASCO) study protocol. *Int J Stroke*. 2012;7(4):341–347.
13. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864–870.
14. Jorm AF, Christensen H, Korten AE, et al. Informant ratings of cognitive decline in old age: validation against change on cognitive tests over 7 to 8 years. *Psychol Med*. 2000;30(4):981–985.
15. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol*. 1986;5:165–173.
16. Friedman B, Heisel MJ, Delavan RL. Psychometric properties of the 15-item Geriatric Depression Scale in functionally impaired, cognitively intact, community-dwelling elderly primary care patients. *J Am Geriatr Soc*. 2005;53(9):1570–1576.
17. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699.
18. Doniger GM, Dwolatzky T, Zucker DM, et al. Computerized cognitive testing battery identifies mild cognitive impairment and mild dementia even in the presence of depressive symptoms. *Am J Alzheimers Dis Other Demen*. 2006;21(1):28–36.
19. Petersen R. Mayo Clinic office visit, mild cognitive impairment: an interview with Ronald Petersen, MD, PhD. *Mayo Clin Womens Healthsource*. 2006;10(11):7–8.
20. Pendlebury ST, Mariz J, Bull L, et al. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. *Stroke*. 2012;43(2):464–469.
21. Ivnik RJ, Haaland KY, Bieliauskas LA. American Board of Clinical Neuropsychology special presentation: the American Board of Clinical Neuropsychology (ABCN), 2000 update. *Clin Neuropsychol*. 2000;14(3):261–268.
22. Stuart M, Turman AB, Shaw J, et al. Effects of aging on vibration detection thresholds at various body regions. *BMC Geriatr*. 2003;3(1):1.

23. Dwolatzky T, Whitehead V, Doniger GM, et al. Validity of the Mindstreams computerized cognitive battery for mild cognitive impairment. *J Mol Neurosci*. 2004;24(1):33–44.
24. Duncan PW, Bode RK, Min Lai S, et al; Glycine Antagonist in Neuroprotection Americans Investigators. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. *Arch Phys Med Rehabil*. 2003;84(7):950–963.
25. Stark SL, Edwards DF, Hollingsworth H, et al. Validation of the Reintegration to Normal Living Index in a population of community-dwelling people with mobility limitations. *Arch Phys Med Rehabil*. 2005;86(2):344–345.
26. Artzi M, Aizenstein O, Jonas-Kimchi T, et al. FLAIR lesion segmentation: application in patients with brain tumors and acute ischemic stroke. *Eur J Radiol*. 2013;82(9):1512–1518.
27. Wahlund LO, Barkhof F, Fazekas F, et al; European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32(6):1318–1322.
28. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35–41.
29. Burn JP. Reliability of the modified Rankin Scale. *Stroke*. 1992;23(3):438.
30. Allan LM, Rowan EN, Firbank MJ, et al. Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. *Brain*. 2011;134(Pt 12):3716–3727.
31. Parikh RM, Robinson RG, Lipsey JR, et al. The impact of poststroke depression on recovery in activities of daily living over a 2-year follow-up. *Arch Neurol*. 1990;47(7):785–789.
32. Willey JZ, Disla N, Moon YP, et al. Early depressed mood after stroke predicts long-term disability: the Northern Manhattan Stroke Study (NOMASS). *Stroke*. 2010;41(9):1896–1900.
33. Kauhanen M, Korpelainen JT, Hiltunen P, et al. Poststroke depression correlates with cognitive impairment and neurological deficits. *Stroke*. 1999;30(9):1875–1880.
34. Steffens DC, Otey E, Alexopoulos GS, et al. Perspectives on depression, mild cognitive impairment, and cognitive decline. *Arch Gen Psychiatry*. 2006;63(2):130–138.
35. Rosenberg PB, Mielke MM, Xue QL, et al. Depressive symptoms predict incident cognitive impairment in cognitive healthy older women. *Am J Geriatr Psychiatry*. 2010;18(3):204–211.
36. Rosenberg PB. Clinical aspects of inflammation in Alzheimer's disease. *Int Rev Psychiatry*. 2005;17(6):503–514.
37. Hayden KM, Zandi PP, Lyketsos CG, et al; Cache County Investigators. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. *Alzheimer Dis Assoc Disord*. 2006;20(2):93–100.
38. Bremmer MA, Deeg DJ, Beekman AT, et al. Major depression in late life is associated with both hypo- and hypercortisolemia. *Biol Psychiatry*. 2007;62(5):479–486.
39. Hou WH, Liang HW, Hsieh CL, et al. Effects of stroke rehabilitation on incidence of poststroke depression: a population-based cohort study. *J Clin Psychiatry*. 2013;74(9):e859–e866.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Erika F. H. Saunders, MD, at esaunders@psychiatrist.com.