Gait Measures as Predictors of Poststroke Cognitive Function
Evidence From the TABASCO Study

Einor Ben Assayag, PhD; Shani Shenhar-Tsarfaty, PhD; Amos D. Korczyn, MD; Efrat Kliper, MSc; Hen Hallevi, MD; Ludmila Shopin, MD; Eitan Auriel, MD; Nir Giladi, MD; Anat Mike, MA; Anat Halevy, MA; Aner Weiss, BSc; Anat Mirelman, PhD; Natan M. Bornstein, MD*; Jeffrey M. Hausdorff, PhD*

Background and Purpose—Patients with stroke are at risk for developing cognitive impairment. We tested whether the assessment of balance and gait can enhance the prediction of long-term cognitive outcome in stroke survivors.

Methods—Participants were patients with first-ever, mild-moderate ischemic stroke or transient ischemic attack from the Tel Aviv Brain Acute Stroke Cohort (TABASCO) study, a large prospective cohort study, who underwent 3-T MRI and were followed for ≥2 years using neurological, neuropsychological, and mobility examinations 6, 12, and 24 months after the index event.

Results—Data were available for 298 patients (age: 66.7±9.6 years). Forty-six participants (15.4%) developed cognitive decline (CD) over the 2 years of follow-up. The CD group and cognitively intact group did not differ in their neurological deficits or in their infarct volume or location. Nonetheless, 6 months after stroke, the Timed Up and Go test took longer in those who later developed CD (P<0.001). Additionally, the CD group also had lower Berg Balance Scale scores (P<0.001), slower gait (P<0.001), and fewer correct answers during dual-task walking (P=0.006). Separate analyses of the patients with transient ischemic attack revealed similar results. Multivariate regression analysis showed that Timed Up and Go times ≥12 s at 6 months after stroke/ transient ischemic attack was a significant independent risk marker of CD 24 months after stroke (odds ratio=6.07, 95% confidence interval: 1.36–27.15).

Conclusions—These results suggest that measures of balance and gait are significant risk markers of cognitive status 2 years after stroke. Relatively simple, performance-based tests of mobility may enhance the identification of stroke/transient ischemic attack survivors who have an increased risk of developing CD.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01926691.

(Stroke. 2015;46:1077-1083. DOI: 10.1161/STROKEAHA.114.007346.)

Key Words: gait ◼ mild cognitive impairment ◼ stroke

Stroke considerably increases the risk of cognitive decline (CD) and dementia, with prevalence rates ranging from 24% to 33.3% within 5 years from stroke onset. In many cases, the cognitive decline develops abruptly, while in others, the decline develops insidiously over months or years at a rate which far exceeds the expected decline in this age group.1,2 After a stroke, patients frequently experience a spectrum of neuropsychological and motor deficits that can significantly interfere with their cognitive, communicative, and motor functions, resulting in impaired activities and function. Identifying those at higher risk of developing cognitive impairment has implications for the early initiation of treatment and for monitoring disease progression.

Slowing of motor function is commonly observed with aging and is more pronounced in cognitively impaired individuals.3 Gait changes predict dementia as much as 6 to 10 years later4 and may also precede the onset of even mild cognitive impairment,4 which may occur as much as 12 years before the clinical presentation of cognitive changes.5 Moreover, the combination of motor and cognitive changes apparently is a stronger predictor of dementia than cognitive changes alone.6 Although the mechanisms of these motor-cognitive interactions are not fully understood, subclinical pathological changes caused by cerebrovascular disease may

Received September 7, 2014; final revision received January 5, 2015; accepted January 7, 2015.

From the Stroke Unit and the Center for the Study of Movement, Cognition and Mobility, Department of Neurology, Tel Aviv Medical Center, Tel Aviv, Israel (E.B.A., S.-S.T., E.K., H.H., L.S., E.A., N.G., A. Mike, A.H., A.W., A. Mirelman, N.M.B.); and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (E.B.A, A.D.K., E.K., H.H., E.A., N.G., N.M.B., J.M.H.).

*Drs Bornstein and Hausdorff contributed equally.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.orglookup/suppl/doi:10.1161/STROKEAHA.114.007346/*DC1.

Correspondence to Natan M. Bornstein, MD, Department of Neurology, Tel Aviv Medical Center, 6 Weizmann St, Tel Aviv, Israel. E-mail strokeun@tlvmc.gov.il

© 2015 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.007346
play a role. The present study explored the possibility of using measures of balance and gait to augment the prediction of CD in poststroke patients.

Methods

Study Population

Patients were eligible for the present study if they had mild to moderate first-ever acute ischemic stroke or transient ischemic attack (TIA) and were participating in the prospective cohort Tel Aviv Brain Acute Stroke Cohort (TABASCO) study. Patients were excluded if they had hemorrhagic stroke, stroke resulting from trauma or invasive procedures, severe aphasia, CD/dementia, or were unlikely to be discharged from hospital, or to participate in follow-up. All participants signed informed consent forms, approved by the local ethics committee. The neurological assessment included verification of stroke pathogenesis and the National Institutes of Health Stroke Scale (NIHSS). Individuals whose baseline cognitive results were not available and patients who had gait dysfunction after the stroke were excluded.

Cognitive Assessments and Criteria for Cognitive Decline

Detailed cognitive assessment methods are provided in the online-only Data Supplement.

Gait and Balance Protocol

Gait was tested under 2 conditions: (1) Usual walking with no dual-task: Participants were instructed to walk at their normal speed for 1 minute and were allowed to use assistive devices as necessary. (2) Attention-demanding dual-task: Subjects were asked to perform serial subtractions of 3 from 100, during 1 minute while walking. Gait speed was determined by measuring the average time the subject walked the middle 10 m of the 20-m corridor. The Timed Up and Go test (TUG),8 the time to get up from a chair, walk 3 m, turn around, walk back, and sit back down are measured. The Berg Balance Scale (BBS)9 is a physical performance measure that includes 14 items designed to assess both static and dynamic balance. Gait and balance evaluations were measured at 6, 12, and 24 months after the event by trained assessors who were blind to the cognitive data.

Calculation of Ischemic Lesions Volume and White Matter Lesion Score

Detailed neuroimaging methods are provided in the online-only Data Supplement.

Statistical Analysis

Detailed statistical methods are provided in the online-only Data Supplement.

Results

Participants

Between April 1, 2008, and December 31, 2011, 468 consecutive patients were admitted to the Tel Aviv Medical Center within 72 hours after symptom onset with a final diagnosis of TIA or minor stroke, defined by NIHSS <17 at admission, and met inclusion/exclusion criteria. Included patients did not significantly differ on basic demographical and clinical characteristics from those who were excluded.

Among the 468 that were included, 298 subjects had both neuropsychological data at admission and 24 months after the index event, as well as gait and balance data (Figure I in the online-only Data Supplement). Participants who were excluded from the analysis because of absence of neuropsychological or gait and balance data did not differ significantly from those who entered the analysis in age, years of education, NIHSS, hypertension, diabetes mellitus, or dyslipidemia (P=0.06, P=0.113, P=0.676, P=0.218, P=0.775, P=0.816, respectively).

The 298 subjects who were the basis of our analysis had a mean age of 66.7±9.6 years and 62.4% were male; 90 (30.2%) were diagnosed as TIA. Most subjects had a mild stroke (median NIHSS=2). The etiologies were 121 lacunar stroke (58.2%), 21 large-artery atherosclerotic stroke (10.1%), 32 cardioembolic stroke (15.4%), and 34 stroke of other or undetermined pathogenesis (16.3%). No differences in baseline gait and balance measures were observed between stroke subtypes, and they were, therefore, grouped together for further analyses. Table 1 presents the baseline characteristics of all participants. Table 2 describes the patients with TIA separately.

Cognitive Performance

Immediately after the acute event, cognitive scores for most of the patients (TIA and stroke) were <6 months later (23.9±3.3 versus 25.3±3.3, P<0.001 for the Montreal cognitive assessment scores; 92.5±14.1 versus 94.8±12.4, P<0.001 for the computerized global cognitive score). This transient cognitive impairment could be because of the effects of the stroke itself or to nonspecific changes such as stress and insomnia associated with hospital admission.

Forty-six participants (15.4%) developed clinically significant CD during the 2 year of follow-up. The CD group was older and less educated, and their baseline cognitive scores were lower than those of the cognitive intact (CI) group (Table 1). The 2 groups did not differ in their neurological deficits, measured by NIHSS, at hospital admission or 6 months later, or in their infarct volume or lesion location. Nonetheless, TUG test times at 6 months after the acute stroke/TIA were significantly longer in the CD group than in the CI group (CD: 13.4±4.4 s; CI: 10.2±4.4 s; P<0.001). The CD group also had lower (worse) scores on the BBS (CD: 49.2±8.2; CI: 52.7±6.7; P<0.001), reduced gait speed (CD: 0.9±0.2 m/s; CI: 1.3±0.2 m/s; P<0.001), and fewer correct count answers during dual-task walking (CD: 16.3±10.6; CI: 21.3±9.3; P=0.006).

Separate analysis of the patients with TIA revealed that 10 patients out of 90 (11%) developed CD during the 2 years follow-up. As in the combined cohort, the CD TIA group was older and less educated than the CI group (Table 2). Additionally, although they were all discharged from hospital without any neurological deficit or gait dysfunction, their TUG test times 6 months after the event were longer in the CD group compared with the CI group (13.9±5.9 versus 9.1±2.3 s; P<0.001). The CD group also had worse BBS scores (CD: 50.5±3.7; CI: 53.9±4.6; P=0.024), but no significant differences were observed in gait speed or in the number of correct subtractions during dual-task walking (NCSDTW).

Gait and Balance as Predictors of CD

In receiver operating characteristic curve analysis focusing exclusively on the gait and balance variables at 6 months, the
Table 1. Baseline Characteristics of Poststroke/TIA Survivors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants</th>
<th>Cognitive Intact</th>
<th>Cognitive Decline* 2 yr After Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>298</td>
<td>252</td>
<td>46</td>
</tr>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>66.7 (9.6)</td>
<td>65.6 (9.2)</td>
<td>72.3 (9.5)†</td>
</tr>
<tr>
<td>Sex, males (%)</td>
<td>186 (62.4)</td>
<td>162 (64.3)</td>
<td>24 (52.2)</td>
</tr>
<tr>
<td>Education, yr</td>
<td>13.2 (3.7)</td>
<td>13.5 (3.6)</td>
<td>11.8 (3.8)‡</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.6 (4.5)</td>
<td>27.6 (4.5)</td>
<td>27.6 (4.2)</td>
</tr>
<tr>
<td>Not performed MRI</td>
<td>55 (18.5%)</td>
<td>45 (17.9%)</td>
<td>10 (21.7%)</td>
</tr>
<tr>
<td><strong>Lesion location, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New lesion in MRI</td>
<td>160 (56.8)</td>
<td>135 (56.2)</td>
<td>25 (69.4)</td>
</tr>
<tr>
<td>Left hemispheric</td>
<td>69 (43.1)</td>
<td>57 (42.2)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Right hemispheric</td>
<td>57 (35.6)</td>
<td>49 (36.3)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>6 (3.8)</td>
<td>5 (3.7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Brain stem/cerebellium</td>
<td>28 (17.5)</td>
<td>24 (17.8)</td>
<td>4 (16)</td>
</tr>
<tr>
<td><strong>Vascular risk factors or medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>64 (21.5)</td>
<td>53 (21.1)</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>31 (10.4)</td>
<td>25 (9.9)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>159(53.4)</td>
<td>133 (52.8)</td>
<td>26 (56.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>178 (59.7)</td>
<td>146 (57.9)</td>
<td>32 (69.6)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>50 (16.8)</td>
<td>38 (15.1)</td>
<td>12 (26.1)‡</td>
</tr>
<tr>
<td>Number of cardiovascular risk factors, median (IQR)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>Physical activity, minutes/week</td>
<td>204.1 (161.4)</td>
<td>206.5 (166.8)</td>
<td>186.3 (115.9)</td>
</tr>
<tr>
<td>APOE ε4 allele, n (%)</td>
<td>48 (16.1)</td>
<td>39 (15.5)</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>Admission NIHSS, median (IQR)</td>
<td>2 (0–3)</td>
<td>2 (0–3)</td>
<td>2 (0–5)</td>
</tr>
<tr>
<td>Modified Rankin score, 6 mo after stroke, median (IQR)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>1 (0–1.25)‡</td>
</tr>
<tr>
<td>Infarct volume, mm³, (SE)*</td>
<td>2047.4 (4.9)</td>
<td>1950.7 (4.9)</td>
<td>2749.2 (5.3)</td>
</tr>
<tr>
<td>White matter lesion score, median (IQR)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>2 (1–3)‡</td>
</tr>
<tr>
<td>White matter hyperintensities, % intracranial volume</td>
<td>0.3 (0.4)</td>
<td>0.2 (0.4)</td>
<td>0.4 (0.7)</td>
</tr>
<tr>
<td>History of depression, n (%)</td>
<td>32 (10.8)</td>
<td>24 (9.5)</td>
<td>8 (17.4)</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar, %</td>
<td>133 (44.6)</td>
<td>117 (46.4)</td>
<td>16 (34.8)</td>
</tr>
<tr>
<td>Large-artery atherosclerosis, %</td>
<td>33 (11.1)</td>
<td>24 (9.5)</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>Cardioembolic stroke, %</td>
<td>54 (18.1)</td>
<td>47 (18.7)</td>
<td>7 (15.2)</td>
</tr>
<tr>
<td>Other/undetermined pathogenesis, %</td>
<td>78 (26.2)</td>
<td>64 (25.4)</td>
<td>14 (30.4)</td>
</tr>
<tr>
<td><strong>Cognitive scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission MoCA score</td>
<td>23.9 (3.3)</td>
<td>24.3 (3.1)</td>
<td>21.8 (3.6)†</td>
</tr>
<tr>
<td>6 mo MoCA score</td>
<td>25.3 (3.3)</td>
<td>25.7 (3)</td>
<td>22.9 (3.9)†</td>
</tr>
<tr>
<td>Admission computerized global cognitive score</td>
<td>92.5 (14.1)</td>
<td>93.6 (13.7)</td>
<td>86 (15.2)‡</td>
</tr>
<tr>
<td>6 mo computerized global cognitive score</td>
<td>94.8 (12.4)</td>
<td>96.1 (11.8)</td>
<td>87 (13.5)†</td>
</tr>
</tbody>
</table>

(Continued)

highest overall accuracy (area under receiver operating characteristic curve, c-index) in prediction of CD was found for TUG (c=0.722), the second highest for gait speed (c=0.716), the third highest for NCSDTW (c=0.633), and the lowest for BBS (c=0.627). We searched for cutoff points of 6 months poststroke measures that could predict CD during the remaining follow-up with a sensitivity of ≥85% combined with the best possible specificity. For TUG, the value of 12 s was identified as such a cutoff point. For NCSDTW, the value of 15 correct answers, for gait speed the value of 1.0 m/s, and for the BBS the value of 50 were identified as such cutoff points. The receiver operating characteristic curves demonstrated that corresponding to practically any fixed level of sensitivity, the specificity of the TUG in predicting CD during the follow-up stayed higher than the specificity of NCSDTW, gait speed, or BBS.

Univariate and Multivariate Predictors of Cognitive Impairment or Dementia

During the 2 years follow-up period, 46 participants developed CD (either before death or currently alive with dementia, n=8, or cognitive impairment, n=38). Two of them were diagnosed as cognitive decliners during the first 6 months and were therefore excluded from the analyses that evaluated the contribution of gait and balance measures at 6 months after the admitting event to future CD.

Significant univariate predictors of poststroke CD (cognitive impairment or dementia) during the 2 years are shown in Table 3. Significant predictors included the 6 months cognitive scores, age, TUG score, NCSDTW, BBS score, lower education (<12 years), white matter lesion score, and Modified Rankin score at 6 months. In multivariate analysis, predictors retained were age, cognitive scores, and the TUG as assessed at 6 months after the incident event (Table 3). The BBS scores and the NCSDTW did not survive as significant independent predictors in the multivariate analysis. The Figure (A) shows the survival curve to CD according to TUG times at 6 months after stroke.
Longitudinal changes in computerized global cognitive score (NeuroTrax) according to TUG results at 6 months are shown in Figure (B). At that time point, 62 subjects performed the TUG in >12 s (the 13.5-s threshold has been indicated as a high risk of falls and a cutoff point of 12 s has been applied to identify normal mobility in 413 community-dwelling elderly\textsuperscript{10}). The difference between the curves was significant (P<0.001), as assessed by repeated measurements ANOVA.

**Associations Between Gait and Balance Variables and Cognitive Performance**

Associations between gait and balance at 6 months with cognitive scores, adjusted for age and sex, are shown in Table I in the online-only Data Supplement. The outcomes with the highest correlation to 24 months cognitive scores were TUG (correlation with Montreal cognitive assessment, r=-0.40,
P<0.001 and with the computerized global cognitive score [NeuroTrax], \( r=-0.26, P=0.027 \), gait speed (with Montreal cognitive assessment, \( r=-0.47, P<0.001 \) and with global cognitive score, \( r=-0.42, P<0.001 \), and NCSDTW (with Montreal cognitive assessment, \( r=0.28, P=0.017 \), with global cognitive score, \( r=0.42, P<0.001 \), Memory score, \( r=0.41, P<0.001 \) and Executive function score \( r=0.37, P=0.002 \)). Associations of neurological status (NIHSS) or infarct volume with poststroke cognitive scores were weaker (Table I in the online-only Data Supplement).

**Discussion**

Our results suggest that balance and gait are significant risk markers for cognitive status and impaired cognitive recovery after mild stroke or TIA. We found that 15.4% of the participants developed poststroke CD between 6 and 24 months after the stroke. In the meta-analysis of poststroke dementia in 22 separate cohorts,\(^2\) the prevalence of poststroke dementia ≤1 year was 20.3% in hospital-based studies, substantially higher than in our cohort. However, the studies in that meta-analysis included severe and recurrent strokes and early poststroke dementia (at 3 months), in whom dementia may have begun before the stroke. In contrast, we included only mild to moderate, first-ever stroke/TIA, free of dementia at admission.

The CD and CI groups did not differ in their neurological deficits but differed significantly in all balance and gait measures 6 months after stroke. The CD group had longer TUG times, lower BBS scores, lower gait speed, and less correct answers during dual-task walking. The multivariate analyses (Table 3) suggest that TUG test times at 6 months after stroke is a significant, independent risk marker of long-term incidence of dementia/CD, in addition to the known risk factors of age and cognitive state at baseline. However, these findings need to be confirmed in larger studies. APOE ε4 allele was...
not associated with CD, but this may have been because of the sample size.

The TUG is a widely used test for assessing functional mobility and is also considered useful in the clinical assessment of change in functional status. The test is quick to administer, requires no special equipment or training, and is easily included as part of routine medical examination. Recently, a few groups examined the relationship between TUG and cognitive performance. Greene and colleagues focused on change in test results over time in 189 community dwelling older adults. They reported that TUG and the BBS scores were not significantly associated with CD after 2 years follow-up, but rather the change from baseline to follow-up in TUG parameters was independently and significantly associated with CD. It is possible that in our population the stroke may have triggered or unmasked underlying neurodegenerative processes. In most cases, however, the cerebrovascular changes in the brain appeared to explain poststroke CD better than only the presence of primary neurodegenerative disease pathology. We, therefore, suggest that in most of the decliners, the stroke may have triggered or hastened cognitive deterioration in a cause and effect manner.

The mobility parameters that we examined here may be sensitive risk markers of cognitive changes, distinct from the general motor slowing that was demonstrated by gait speed in the poststroke population. This relationship can be explained by the idea that the TUG relies on the interplay between attention, executive function, and motor processing functions. Moreover, dual-task during gait may be a marker of the efficiency of the central integration of multiple cognitive domains needed for this complex task.

Several studies have examined baseline gait speed and other motor signs as predictors of the future development of cognitive impairment. To our knowledge, no study has prospectively examined mobility measures as predictors of CD in stroke survivors. The heterogeneity of the impact of the stroke in terms of lesion size and location, one might have anticipated that the motor signs may not necessarily predict CD. Nonetheless, the present results suggest that in this population, motor control abilities, at least certain motor control features, may be helpful in identifying subjects who are more likely to experience cognitive deterioration over time.

A major strength of this study is the systematic follow-up with careful prospective surveillance of mobility and cognitive performance. This allowed us to document the temporal nature of possible CD after stroke. The main limitation of the current study is the absence of a control group. However, the purpose of this study was to conduct an exploratory investigation of the interactions between mobility measures and prediction of cognitive performance after stroke. In a sense, each subject served as a control and his/her performance has been compared at the different time points. Second, we included only patients with mild clinical stroke manifestations. We chose to focus on patients who are expected to be able to perform cognitive tests, to ambulate, and to be available for follow-up, with low drop-out rates. Those patients are less likely to experience noncognitive deficits after stroke, which might influence their performance in cognitive testing. To address further additional, future deterioration and the later development of dementia, we plan to continue the follow-up on those patients. Third, because volumetric measures of white matter lesion were available for only part of the cohort, a semiquantitative score determined white matter lesion load. This may have limited our ability to control for lesion load. It is, nonetheless, important to keep in mind the results of previous studies which found strong correlations between volumetric measures and the semiquantitative scoring.

Poststroke patients with cognitive impairments can significantly benefit from rehabilitation. Today, there is widespread awareness that a connection exists between neuropsychological and motor domains, although this is not yet fully understood. Although additional study is needed, the present findings suggest that tests of motor function may enhance the identification of those stroke survivors who have an increased risk of developing CD and enable early adaption of prevention and rehabilitation strategies to delay the onset of CD and dementia in an at-risk population.

Acknowledgments
We thank Dr Ely Simon and Dr Glen Doniger, NeuroTrax Corp, for the use of the computerized neuropsychological tests and their advice.

Sources of Funding
This study is supported by grant 3000000-5062 from the Ministry of Health Israel; RAG11482 from the American Federation for Aging Research (AFAR) and 2011344 from the US—Israel Binational Science Foundation (BSF). Statistical analyses were conducted by E. Ben Assayag, PhD, Tel Aviv Medical Center.

Disclosures
None.

References


Gait Measures as Predictors of Poststroke Cognitive Function: Evidence From the TABASCO Study

Stroke. 2015;46:1077-1083; originally published online February 12, 2015;
doi: 10.1161/STROKEAHA.114.007346
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/4/1077

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/02/13/STROKEAHA.114.007346.DC1
http://stroke.ahajournals.org/content/suppl/2016/04/06/STROKEAHA.114.007346.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL

Gait measures as predictors of post-stroke cognitive function: Evidence from the TABASCO study

Supplemental Methods

Baseline and follow-up cognitive assessments
All participants were reportedly free from cognitive decline/dementia before the stroke/transient ischemic attack (TIA) (as determined by using the Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE). An IQCODE score <3.3 was considered cognitively intact). Patients completed a baseline neuropsychological assessment within 72-96 hours from stroke symptoms onset including the Montreal Cognitive Assessment (MoCA) and the NeuroTrax computerized cognitive test battery (NeuroTrax Corp., Houston, TX) that assesses an array of cognitive domains (i.e., memory, executive functions, visuospatial perception, verbal function and attention). Neuropsychological evaluations were repeated at 6, 12 and 24 months after the event.

Criteria for cognitive decline
All evaluations were based on a neurological and general clinical examinations, cognitive scores and the evaluation of activities of daily life (ADL) using the ADL domain in the Stroke Impact Scale (SIS), after an interview with the patient and his/her family. Patients with cognitive decline were diagnosed as having either mild cognitive impairment (MCI) or dementia. In order to diagnose MCI, the modified Petersen criteria were applied: the subject had to be impaired (>1.5 SD) on at least 1 cognitive domain compared with age and education norms on the MoCA score, to have no impairment of basic functional activities, as measured by the SIS-ADL, and to not fulfill the DSM IV-TR criteria for dementia.

The norms for each test of the NeuroTrax computerized cognitive testing were previously published (http://www1.neurotrax.com/docs/norms_guide.pdf) and fit to an age and education normed IQ-style scale with a mean of 100.0 and a standard deviation of 15.0. Cognitive decline from baseline to follow-up examinations was determined. Participants who could not complete the MoCA or whose cognitive results had fallen by >1.5 SD in the MoCA and/or the NeuroTrax scores between baseline and/or between the 6 months post-stroke assessment to any of the follow-up assessments, and/or had other evidence or suspicion of dementia/cognitive decline, judged by a cognitive neurologist, were referred to a senior clinician (ADK) to determine whether the participant met the DSM IV-TR criteria for dementia. Assessments were reviewed by a consensus forum that included the assessor, 3 senior neurologists specializing in memory disorders, and a neuropsychologist. Subjects who met criteria for MCI or dementia were grouped together as "cognitive decline" (CD).

Calculation of ischemic lesions volume
All images were acquired within 7 days of stroke onset on a 3T GE scanner using an 8-channel head coil. Presence of acute ischemic infarcts was assessed by a senior neuro-radiologist, based on the diffusion weighted imaging (DWI). Volumes (in mm$^3$) of ischemic lesions were calculated across the whole brain and the quantification of the ischemic lesions was performed using a semi-automatic method, without knowledge of the clinical data.
White matter lesion (WML) score
WML were identified on FLAIR scans and rated semiquantitatively based on a 3-point scale according to the periventricular score of Fazekas-Wahlund for white matter lesions.\textsuperscript{9}
**Statistical analysis**

To examine the associations between balance and gait and risk for cognitive decline or dementia, Cox proportional regression analyses were used to obtain univariate proportional hazard ratios for each balance and gait parameter with time (months) from index stroke to cognitive decline or dementia as the dependent variable. The date of onset of cognitive decline or dementia was assumed to be at the midpoint between the two assessments where cognitive status was assessed. Hazard ratios were given according to presence or absence of the risk factor, or per point on quantitative scales, as appropriate. Following identification in univariate models, significant predictors of cognitive decline were entered into a multivariate forward stepwise Cox regression model, p<0.05 for entry, p>0.1 for removal.

A measure of goodness-of-fit was used to evaluate the fit of a logistic regression model based on the simultaneous measure of sensitivity (true positive) and specificity (true negative) for all possible cutoff point. First, we calculated the sensitivity and specificity pairs for each possible cutoff point using the receiver operating characteristic (ROC) curve. The ROC curve was used in the search of the optimal cut-off points for each mobility variable for the prediction of cognitive decline (MCI or dementia) during the follow-up. Further, repeated analysis-of-variance techniques were used to compare cognitive scores by the optimal cutoff value of mobility results at 6, 12 and 24 months. Results from cognitive scores of groups of mobility results by the optimal cutoff value were compared using a repeated-measurements Analysis of covariance (ANCOVA). Comparisons or distributions between categories and numeric variables were assessed using the Student's t-test, the Mann–Whitney U test or chi square analysis, as appropriate. Associations between numeric variables were determined using the Pearson or Spearman’s rank correlation analysis. Since the volumes of both ischemic lesions and WML were skewed, a logarithmic transformation was applied aiming to normalize the distributions. Statistical differences between longitudinal cognitive curves of the different groups (high and low dual-task or TUG test results) were analyzed by a two-way Analysis of variance (ANOVA), and post hoc analyses were performed using the Bonferroni test. A p-value of less than 0.05 was considered statistically significant. SPSS software version 19 was used for all statistical analyses.
Supplemental Results

Supplemental Figure I Legend: Flow chart of patient selection

Enrolled stroke/TIA patients without baseline gait or cognitive dysfunction after stroke: n=470

Baseline computerized neuropsychological data missing n=82

Eligible n=388

Deceased before their first follow-up examination of cognitive status: n=14

Baseline (6m) gait measures missing: n=34

Endpoint (24m) computerized neuropsychological data missing 24 months: n=42

Baseline and 24 months neuropsychological data (or follow-up examination of cognitive status before death) and both balance and gait measures at 6 and 24 months available: n=298

Supplemental Figure I
**Supplemental Table I:** Partial correlations (adjusted for age and gender) between mobility variables and cognitive scores 6 and 24 months post-stroke

<table>
<thead>
<tr>
<th></th>
<th>At 6 months post-stroke/TIA</th>
<th></th>
<th></th>
<th>At 24 months post-stroke/TIA</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MoCA</td>
<td>Global cognitive score</td>
<td>Memory score</td>
<td>Executive score</td>
<td>MoCA</td>
<td>Global cognitive score</td>
</tr>
<tr>
<td>Berg Balance Score</td>
<td>.316**</td>
<td>.232*</td>
<td>.148</td>
<td>.002</td>
<td>.348**</td>
<td>.334**</td>
</tr>
<tr>
<td>Timed Up and Go time</td>
<td>-.425**</td>
<td>-.265*</td>
<td>-.120</td>
<td>-.154</td>
<td>-.398**</td>
<td>-.258*</td>
</tr>
<tr>
<td>Usual Gait speed</td>
<td>.509**</td>
<td>.432**</td>
<td>.282*</td>
<td>.252*</td>
<td>.470**</td>
<td>.416**</td>
</tr>
<tr>
<td>No. of correct answers (during dual-task)</td>
<td>.295*</td>
<td>.374**</td>
<td>.323**</td>
<td>.346**</td>
<td>.279*</td>
<td>.416**</td>
</tr>
<tr>
<td>NIHSS</td>
<td>-.165</td>
<td>-.334**</td>
<td>-.298*</td>
<td>-.357**</td>
<td>-.291*</td>
<td>-.330**</td>
</tr>
<tr>
<td>Infarct volume</td>
<td>-.113</td>
<td>-.288*</td>
<td>-.262*</td>
<td>-.208</td>
<td>-.282*</td>
<td>-.249*</td>
</tr>
</tbody>
</table>

*p<.05, **p<.001, §Results from NeuroTrax computerized cognitive testing.

TIA, transient ischemic attack, NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment.
Supplemental References:

1. Jorm AF, Christensen H, Korten AE, Jacomb PA, Henderson AS. Informant ratings of cognitive decline in old age: Validation against change on cognitive tests over 7 to 8 years. *Psychol Med*. 2000;30:981-985


Gait Measures as Predictors of Poststroke Cognitive Function
Evidence From the TABASCO Study
Einor Ben Assayag, PhD 1,2; Shani Shenhar-Tsarfaty 1, PhD; Amos D. Korczyn, MD 2, et al.

1 Stroke Unit and the Center for the Study of Movement, Cognition and Mobility, Department of Neurology, Tel Aviv Medical Center, Tel Aviv, Israel; and 2 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Stroke 2015; 46: 1077-1083. DOI: 10.1161/STROKEAHA.114.007346.