Clinical Prediction of Fall Risk and White Matter Abnormalities

A Diffusion Tensor Imaging Study

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Background: The Tinetti scale is a simple clinical tool designed to predict risk of falling by focusing on gait and stance impairment in elderly persons. Gait impairment is also associated with white matter (WM) abnormalities.

Objective: To test the hypothesis that elderly subjects at risk for falling, as determined by the Tinetti scale, have specific patterns of WM abnormalities on diffusion tensor imaging.

Design, Setting, and Patients: Community-based cohort of 125 homebound elderly individuals.

Main Outcome Measures: Diffusion tensor imaging scans were analyzed using tract-based spatial statistics analysis to determine the location of WM abnormalities in subjects with Tinetti scale scores of 25 or higher (without risk of falls) and lower than 25 (with risk of falls). Multivariate linear least squares correlation analysis was performed to determine the association between Tinetti scale scores and local fractional anisotropy values on each skeletal voxel controlling for possible confounders.

Results: In subjects with risk of falls (Tinetti scale score <25), clusters of abnormal WM were seen in the medial frontal and parietal subcortical pathways, genu and splenium of corpus callosum, posterior cingulum, prefrontal and orbitofrontal pathways, and longitudinal pathways that connect frontal-parietal-temporal lobes. Among these abnormalities, those in medial frontal and parietal subcortical pathways correlated with Mini-Mental State Examination scores, while the other locations were unrelated to these scores.

Conclusions: Elderly individuals at risk for falls as determined by the Tinetti scale have WM abnormalities in specific locations on diffusion tensor imaging, some of which correlate with cognitive function scores.

We investigated the hypothesis that elderly subjects at risk for falling as determined by the Tinetti scale would have specific patterns of WM abnormalities on diffusion tensor imaging (DTI). We further hypothesized that certain patterns of DTI abnormalities in these subjects are related to cognitive function and that some are not.

**METHODS**

**SUBJECTS**

The study sample consisted of 173 participants of the Nutrition, Aging, and Memory in Elders study who had magnetic resonance imaging (MRI) evaluations with DTI. The study designs, including the inclusion and exclusion criteria and clinical assessment, have been described in detail previously. Briefly, a subset of 366 subjects from a total of 1246 subjects recruited from Boston’s 3 Aging Services Access Points had detailed psychiatric, neurological, and MRI examinations in addition to the routine nutritional, neuropsychological, medical-historical, and blood chemistry evaluations. The Aging Services Access Points provide services and support for independent living to elderly individuals who are at least 60 years old and have low income, diminish in activities of daily living, and need in a critical area such as food or personal care. The Tufts–New England Medical Center Institutional Review Board approved the study, and all participants signed informed consent. The original DTI sample consisted of 187 subjects, of whom 13 were excluded owing to missing Tinetti scale scores, bookkeeping errors, and, in 1 case, an amputated leg (limiting assessment by the Tinetti scale). Additionally, 42 subjects were excluded owing to insufficient MRI fields of view for covering the whole cortical area, a requirement for the normalization process for tract-based spatial statistics (TBSS) analysis. Six additional subjects were excluded based on Mini-Mental State Examination (MMSE) scores as explained later, leaving a final sample of 125 participants.

**MRI SCANNING AND IMAGE PROCESSING**

All subjects were imaged on a 1.5-T scanner (Siemens Symphony). The DTI was performed using a single-shot, spin-echo, echo-planar sequence and 6 independent directions. Imaging data were preprocessed to extract noise and noncoronal sections. Fractional anisotropy (FA) values were then calculated and put into the TBSS pipeline, where we created a study-specific template and FA skeleton indicating major fiber pathways. All normalized FA data were then projected onto this skeleton. After this projection, statistical processing was done on each overlaid voxel. We determined WM hyperintensity volume and intracranial volumes by using the histogram analysis method.

**HEALTH, NEUROPSYCHOLOGICAL, AND NEUROLOGICAL ASSESSMENTS**

Extensive demographic and laboratory data were collected for each Nutrition, Aging, and Memory in Elders study subject. Participants responded to questions documenting the presence of abnormalities from a list of chronic conditions and health events. Physical functioning was examined using modified activities of daily living. A board-certified psychiatrist evaluated the subjects and recorded the Hamilton Rating Scale for Depression, Clinical Dementia Rating Scale, and MMSE scores (0–30). Six of the 131 subjects with MMSE scores below 21 were excluded from the analysis because of the likelihood of association with moderate to severe dementia. A board-certified neurologist performed neurological evaluations and determined whether the subject had findings of symptomatic stroke and a peripheral neuropathic or spinal cord disorder. A consensus diagnosis of psychiatric and neurological disorders was made at a meeting attended by the study psychiatrist, neuropsychologist, neurologist, and neuroradiologist. Each subject was assigned to any (or none) of the diagnoses of Alzheimer disease (possible or probable), mild cognitive impairment, vascular dementia, and depression according to defined criteria. Subjects were considered to have no cognitive impairment if they were not demented and had scored no more than 1 SD below the mean of age- and education-defined strata on MMSE scores and no more than 1.5 SD below the mean of age- and education-defined strata on neuropsychological tests.

**GAIT ASSESSMENT AND CATEGORIZATION OF TINETTI SCALE SCORES**

Each participant’s gait and balance were assessed during neurological examination including a standardized Tinetti scale. The Tinetti balance and gait evaluation is designed to assess both balance and gait using a simple bedside clinical evaluation scale that has a maximum total score of 28 (16 points for best balance; 12 points for best gait). The balance examination begins with the subject seated in a hard, armless chair, and evaluation of each of 3 broad performance outcomes are made: (1) sitting and rising (0–5 points); (2) standing and turning (0–9 points); and (3) sitting down (0–2 points). The gait examination is conducted after the subject is standing and is asked to walk a distance down a hallway first at a normal pace and then returning at a rapid but safe pace. Gait is evaluated in the following categories: (1) initiation (0–1 point); (2) step morphology (length, height, symmetry, continuity; 0–6 points); and (3) gait trajectory (path, truncal sway or flexion, walking stance; 0–5 points). For the purpose of analysis, subjects with Tinetti scale scores of 25 or higher were considered to be without risk of falls and those with scores lower than 25 were considered to be at risk of falls.

**STATISTICAL ANALYSIS**

All of the demographic and clinical variables were compared between the group without risk of falls and the group with risk of falls. For the TBSS analysis, we used multivariate nonparametric correlation to determine the association between Tinetti scale scores and local FA values on each skeletal voxel controlling for possible confounders such as age, sex, arthritis, neuropathy, stroke, and WM hyperintensity volume. Parkinsonism or any variety of Parkinson disease was present in only 2 subjects and therefore was not used as a confounding variable for analysis. First, the entire range of Tinetti scale scores was used as an independent variable to assess the relationship with FA. Second, relationships between Tinetti scale scores and FA were assessed individually in subjects without and with risk of falls. Finally, the relationship between Tinetti scale scores and FA was assessed in subjects without and with risk of falls who were found to have no cognitive impairment. All TBSS voxelwise statistical analyses were based on a permutation-based inference method for nonparametric statistical thresholding, which corrects for multiple comparisons by using the null distribution of the maximum (across the image) voxelwise test statistics. This approach allows inference on statistical maps in the case of unknown null distribution. Here, 3000 iterations were used to calculate statistical inferences (corrected P < .05) for all statistical analyses.
The demographic, clinical, and imaging characteristics of the subjects are shown in the Table. Of the 125 subjects in the study, 78 had Tinetti scale scores of 25 or higher and were considered without risk of falls; 47 had Tinetti scale scores lower than 25 and were considered with risk of falls. The 2 groups of subjects had no significant differences except for MMSE scores. Although the percentage of those with stroke was higher in those with risk of falls compared with those without risk of falls, the difference did not reach statistical significance ($P = .07$). The MMSE scores were lower in those with risk of falls compared with those without risk of falls ($P = .004$). The percentage of subjects with mild cognitive impairment was slightly higher in those without risk of falls and the percentage of those with Alzheimer disease was slightly higher in those with risk of falls, but neither reached statistical significance.

Significant abnormal FA clusters (representing loss of WM integrity) were seen in the genu of corpus callosum as well as the frontostriatal and temporal part of the superior longitudinal pathway when the entire study population, including the entire range of Tinetti scale scores (without or with risk of falls), was evaluated (Figure 1A).

When subjects were grouped into those without and with risk of falls (high and low Tinetti scale scores), no abnormal WM FA clusters were seen in those without risk of falls (Tinetti scale score $\geq 25$). However, when subjects with risk of falls (Tinetti scale score $< 25$) were evaluated, significant abnormal FA clusters were seen in the medial frontal and parietal peripheral pathways, genu and splenium of corpus callosum, posterior cingulum, prefrontal and orbitofrontal pathways, and the longitudinal pathways that connect frontal-parietal-temporal lobes (Figure 1B). Furthermore, clusters showing correlation between Mini-Mental State Examination (MMSE) and Tinetti scale scores (blue to light blue) are seen in the medial frontal and parietal peripheral pathways (I); MMSE-independent clusters (red to yellow) are seen in the genu and splenium of corpus callosum, posterior cingulum, prefrontal and orbitofrontal pathways (II), and longitudinal pathways that connect frontal-parietal-temporal circuits (III). Green indicates white matter skeleton.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (N=125)</th>
<th>Without Risk of Falls* (n=78)</th>
<th>With Risk of Falls* (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>71.93 (7.83)</td>
<td>71.12 (6.78)</td>
<td>73.30 (9.23)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>91 (72.8)</td>
<td>59 (75.6)</td>
<td>32 (68.1)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>43 (34.4)</td>
<td>25 (32.1)</td>
<td>18 (38.3)</td>
</tr>
<tr>
<td>Arthritis, No. (%)</td>
<td>100 (80.0)</td>
<td>62 (79.5)</td>
<td>38 (80.9)</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>25.79 (2.62)</td>
<td>26.30 (2.48)</td>
<td>24.93 (2.65)</td>
</tr>
<tr>
<td>Stroke, No. (%)</td>
<td>26 (20.8)</td>
<td>12 (15.4)</td>
<td>14 (29.8)</td>
</tr>
<tr>
<td>Neuropathy, No. (%)</td>
<td>86 (68.8)</td>
<td>53 (67.9)</td>
<td>33 (70.2)</td>
</tr>
<tr>
<td>Depression, No. (%)</td>
<td>47 (37.6)</td>
<td>30 (38.5)</td>
<td>17 (36.2)</td>
</tr>
<tr>
<td>Sum of diminishment in</td>
<td>8.84 (7.75)</td>
<td>9.17 (7.41)</td>
<td>9.77 (8.89)</td>
</tr>
<tr>
<td>ADLs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMHIV, mean (SD), L</td>
<td>0.0032 (0.0046)</td>
<td>0.0031 (0.0035)</td>
<td>0.0034 (0.0058)</td>
</tr>
<tr>
<td>NCI, No. (%)</td>
<td>57 (45.6)</td>
<td>33 (42.3)</td>
<td>24 (51.1)</td>
</tr>
<tr>
<td>MCI, No. (%)</td>
<td>38 (30.4)</td>
<td>28 (35.9)</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>AD, No. (%)</td>
<td>14 (11.2)</td>
<td>6 (7.7)</td>
<td>8 (17.0)</td>
</tr>
<tr>
<td>VD, No. (%)</td>
<td>10 (8.0)</td>
<td>7 (9.0)</td>
<td>3 (6.4)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; ADLs, activities of daily living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NCI, no cognitive impairment; VD, vascular dementia; WMHIV, white matter hyperintensity volume.

*Subjects with Tinetti scale scores of 25 or higher were considered without risk of falls; those with Tinetti scale scores less than 25 were considered with risk of falls.

b $P < .01$.
The results of this DTI study in a community-based sample of elderly subjects add to previous clinical and neuroimaging observations. The study shows that subjects who were clinically determined to be at risk for falls by the Tinetti scale had WM abnormalities in specific locations, which were not seen in those who were determined not to be at risk for falls by the same scale. In those with risk of falls, we observed a pattern of WM abnormalities in the medial frontal and parietal peripheral pathways as well as in the genu and splenium of corpus callosum, posterior cingulum, prefrontal and orbitofrontal pathways, and longitudinal pathways that connect frontal-parietal-temporal circuits. We also showed that the WM abnormalities in the medial frontal and parietal subcortical pathways were dependent on the MMSE scores, with a higher probability of finding these lesions in subjects with low MMSE scores. Locations of the other WM abnormalities were unrelated to the MMSE scores. Finally, we also observed that individuals with risk of falls who had no cognitive impairment also had WM abnormalities mostly in the areas shown to be independent of MMSE scores. However, the abnormalities in this group were smaller than those observed in all subjects with risk of falls, likely owing to a smaller number of individuals included for analysis.

Gait assessment has been used in the elderly population for detection of neurodegenerative disorders. A recent longitudinal study showed that gait speed decline can be a useful predictor of mild cognitive impairment up to 10 years before the initial diagnosis is secured.  Most obviously and importantly, gait assessment can be used to evaluate an individual’s risk of falling. Gait assessment can be performed by clinical tools such as the Tinetti scale or by more extensive analysis of gait velocity, stride length, width, and cadence. While the latter approach provides a more quantitative assessment of gait, tools like the Tinetti scale have the advantage of providing quick and simple bedside assessment, albeit at a risk of subjective interpretations. The Tinetti scale has been used independently or as a component of more elaborate clinical fall assessment instruments in which other clinical variables are also considered.

Wide variations are found in the literature in interpretation of the Tinetti scale owing to different scoring systems and cutoff values used to determine its validity and reliability. Nevertheless, the Tinetti scale, which provides information regarding gait and stance of an individual, is found to be an effective tool for assessment of fall risk. The gait and balance subscales of the Tinetti scale have been used separately or in a combined maximum score of 28, with a higher score indicating better mobility function. Using the Tinetti scale, an individual’s risk of falling is considered to be moderate when the score is between 19 and 24 and high when the score is lower than 19. In this study, we used a cutoff score of less than 25 for assessing any fall risk in absence of actual fall data. Using similar cutoff values, previous studies have shown the sensitivity of the Tinetti scale to be about 70% and the specificity to be between 53% and 60% in predicting a fall within 1 year.

Abnormalities of the WM have been described in subjects with gait impairment using both conventional MRI and DTI. In a previous study, using a region-of-interest analysis approach to DTI, we found a significant relationship between Tinetti scale scores and FA in the genu of corpus callosum. This relationship was independent of various other confounders including MMSE scores. In a recent large DTI study, de Laat et al evaluated the relationship between gait function and FA. These investigators found widespread WM abnormalities in almost all regions of commissural, association, and projection fibers related to various gait parameters. In our study, we have further explored the relationship between the Tinetti scale score and gait using a TBSS approach to DTI. Quantitative evaluation of whole-brain WM was possible in this study by using this approach. Furthermore, TBSS analysis ensures minimum bias from including non-WM voxels during the smoothing process and reduces structural variability among the subjects.

The significant relationships between gait, MMSE scores, and WM alterations in frontal connections that we describe here further argue for an anatomical basis for previous suggestions, which considered the bilateral frontal network as a core functional subsystem for both cognitive and gait functioning. In addition, we also observed parietal peripheral abnormalities on DTI that were dependent on MMSE scores. The idea that there is involvement of higher-level neural function in gait is supported by dual-task paradigms showing interference with gait function by loading with a cognitive task and was also shown in a recent functional neuroimaging study. Blahak et al reported an association between the incidence of falls and deep frontal WM hyperintensities on conventional T2-weighted MRI. Our findings confirm...
their observations and are further evidence that these focal abnormalities are related to cognitive function.

We also observed several WM abnormalities in specific locations that were not correlated with a subject’s MMSE scores. The MMSE-independent WM alterations in the genu of corpus callosum observed in this study confirm previous neuroimaging observations of their important role in gait disturbances.\(^{8,9}\) We observed abnormal WM in the splenium of corpus callosum, a finding described previously.\(^{27}\) From these results, the genu and splenium of corpus callosum might be regarded as functioning as a connector hub that provides coordination and interaction between the neural networks within the hemispheres facilitating normal gait. In addition, several other MMSE-independent WM alterations were seen in the association tracts connecting anterior to posterior cortical regions and cortico-pontine-cerebellar pathways. These abnormalities are located within the areas of cortico-cortical and cortico-subcortical connections believed to be responsible for maintenance of normal gait.\(^{6,7}\)

The rationale for dividing study subjects into 2 main categories of those without and with fall risk based on the Tinetti scale score was to identify the specific WM abnormalities that were clinically relevant. While MRI can be used to evaluate a pathoanatomical basis for gait disorders, using it widely for the routine clinical assessment of any patient with gait impairment would be neither practical nor fiscally prudent. The Tinetti scale can be used as a screening tool to select patients for MRI. Our results have shown that patients with a Tinetti scale score of 25 or higher will not show significant WM abnormalities, and MRI is not likely to add relevant information. However, those with Tinetti scale scores lower than 25 have multiple WM abnormalities, and these subjects might benefit from the additional data provided in MRI using tractography.

Our findings suggest that judicious use of MRI can help in improving the sensitivity and specificity of easily accessible and inexpensive clinical evaluation methods of gait and balance such as the Tinetti scale to identify patients at risk for falls. However, before our results from a group of homebound elderly individuals (requiring some assistance for independent living) are generalized, we suggest that our approach might be used as a basis for future studies by longitudinally following the subjects with gait impairment with information on the actual history of falls. Such a study using DTI measures with more directions than the 6 used in this study should enable more accurate fiber tracking for localization of WM abnormalities in relation to specific tracts. By demonstrating brain abnormalities in specific locations on DTI, such studies may help in developing an evidence-based clinical matrix for fall risk consisting of Tinetti scale and cognitive function scores along with other clinical risk factors for falls. Furthermore, this future study might also address the question of whether the use of expensive MRI technology can benefit in guiding specific prevention and rehabilitation strategies for people with gait impairment who are at risk for falls by demonstrating WM abnormalities in specific tracts.\(^{6,38}\)

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