Diffusion Tensor Imaging, White Matter Lesions, the Corpus Callosum, and Gait in the Elderly

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Background and Purpose—Gait impairment is common in the elderly, especially those with stroke and white matter hyperintensities on conventional brain MRI. Diffusion tensor imaging (DTI) is more sensitive to white matter damage than conventional MRI. The relationship between DTI measures and gait has not been previously evaluated. Our purpose was to investigate the relationship between the integrity of white matter in the corpus callosum as determined by DTI and quantitative measures of gait in the elderly.

Methods—One hundred seventy-three participants of a community-dwelling elderly cohort had neurological and neuropsychological examinations and brain MRI. Gait function was measured by Tinetti gait (0 to 12), balance (0 to 16) and total (0 to 28) scores. DTI assessed fractional anisotropy in the genu and splenium of the corpus callosum. Conventional MRI was used to evaluate for brain infarcts and white matter hyperintensity volume.

Results—Participants with abnormal gait had low fractional anisotropy in the genu of the corpus callosum but not the splenium. Multiple regressions analyses showed an independent association between these genu abnormalities and all 3 Tinetti scores ($P<0.001$). This association remained significant after adding MRI infarcts and white matter hyperintensity volume to the analysis.

Conclusions—The independent association between quantitative measures of gait function and DTI findings shows that white matter integrity in the genu of corpus callosum is an important marker of gait in the elderly. DTI analyses of white matter tracts in the brain and spinal cord may improve knowledge about the pathophysiology of gait impairment and help target clinical interventions. (Stroke. 2009;40:3816-3820.)

Key Words: diffusion ■ gait ■ mobility ■ MRI

Maintaining safe walking and balance throughout life is important. Gait impairment is very common in the frail and homebound elderly and its prevalence increases with age.1,2 Falls related to gait impairment are a major cause of morbidity, and fall-related injuries are the sixth leading cause of death in the elderly.3,5 Given the growth of an elderly population in the United States and the world, fall-related injuries are likely to become increasingly common. Therefore, understanding mechanisms of gait impairment in the elderly has become an important public health issue.

The measurable properties of postural stability/balance and gait that are requisite for safe and dependable mobility rely on complex interactions between the central and peripheral nervous systems.6 White matter degeneration has been critically implicated as a major element in the process of aging of the nervous system.7 Strokes, especially due to penetrating artery disease, are the most important cause of white matter gliosis and tissue loss in the elderly. Patients with Binswanger disease often have abnormal gait as well as cognitive and behavioral abnormalities.8 Previous imaging studies using conventional MRI have shown that patients with abnormal gait have significantly more white matter hyperintensities (WMH), brain infarcts, and larger ventricular size on conventional MRI compared with those without gait impairment.2,9–11

Diffusion tensor imaging (DTI) has been shown to be a reliable method for evaluation of white matter integrity and can detect abnormalities in the white matter that appear normal on conventional MRI.12,13 An additional advantage of DTI over conventional MRI is its ability to study individual white matter tracts.14 The relationship between quantitative measures of DTI and gait in an aging population has not been previously evaluated.

We posited that DTI of tracts within the corpus callosum could yield additional information to that gleaned only from analysis of WMH and would reflect the underlying neural
integrity necessary for normal gait, stance, and balance and would correlate with quantitative measures of mobility in the elderly. We explored the corpus callosum because it has been linked to gait function\textsuperscript{15} and is a highly organized coherent bundle of axons that travel in a single direction and as such is ideal for study of white matter integrity through DTI.

Methods

Subjects

The study sample consists of 173 of the 366 participants in the Nutrition, Aging, and Memory in Elders (NAME) study that underwent MRI. The NAME study investigated whether micronutrient status contributed to cognitive impairment and central nervous system abnormalities in elderly subjects.\textsuperscript{16} The study design, including the inclusion–exclusion criteria, was published in detail.\textsuperscript{16} A subset of 366 subjects among the total of 1246 subjects was thoroughly evaluated with psychiatric, neurological examinations and MRI scans in addition to the nutritional, neuropsychological, medical–historical, and blood chemistry evaluations in which all NAME trial subjects participated. The Institutional Review Board approved the NAME study, and all participants signed an informed consent. After Year 1, a DTI sequence was added to the MRI protocol. This report is based on the first consecutive 187 subjects in whom DTI data analysis was completed. Fourteen subjects were excluded: 8 were missing Tinetti scale values, 5 were excluded due to bookkeeping errors, and one was excluded due to an amputated leg. The final sample contained 173 subjects.

Imaging Protocol

All subjects were imaged on a 1.5-Tesla scanner (Siemens Symphony), T1-, intermediate, and T2-weighted axial images were used to determine WMH volume and brain infarcts. DTI was performed using a single-shot, spin echo, echo-planar sequence. DTI data were acquired along 6 independent axes.

Image Analysis

WMH and intracranial volumes were determined by quantitative segmentation using the histogram analysis method described by DeCarli et al.\textsuperscript{17} WMH volumes were reported in liters. A board-certified neuroradiologist determined the presence or absence of MRI infarcts using the method described by the Cardiovascular Health Study.\textsuperscript{18}

DTI images were processed on a Siemens Numaris 4 satellite console (Leonardo workstation) using DTI TASK CARD developed at Massachusetts General Hospital. The region of interest function on this program can be used to determine quantitative DTI information including fractional anisotropy (FA). FA values for the genu and splenium of the corpus callosum were determined by placing elliptical regions of interest in the genu and splenium of corpus callosum (Figure). All regions of interest were placed by a radiology resident and verified by an experienced board-certified neuroradiologist.

Health and Neuropsychological Examination

Extensive demographic, laboratory, and neuropsychological data were collected from NAME participants.\textsuperscript{16} Participants identified their own abnormalities from a list of chronic conditions and health events. Diabetes was defined as the use of antidiabetic medication or fasting glucose $\geq 126$ mg/dL. Hypertension was defined by self-report, systolic pressure $\geq 140$ mm Hg or diastolic pressure $\geq 90$ mm Hg, or use of antihypertension medication. Arthritis was defined as a report of a physician’s diagnosis of arthritis.

Neurological and Psychiatric Examinations

A board-certified psychiatrist evaluated the participants to record the Hamilton Rating Scale for Depression,\textsuperscript{19} the Clinical Dementia Rating Scale,\textsuperscript{20} and the Mini Mental Status Examination (MMSE)\textsuperscript{21} scores.

A neurological evaluation was performed by a board-certified neurologist. All subjects were scored on the National Institutes of Health Stroke Scale.\textsuperscript{22} The neurologist judged whether the subject had clinical evidence of symptomatic stroke(s), peripheral neuropathy, or another neurological syndrome. Strokes were classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria.\textsuperscript{23}

Gait Assessment

Each participant’s gait, balance, and stance were assessed by the neurologist as part of the overall examination using the Performance-Oriented Mobility Assessment scale developed by Tinett.\textsuperscript{24} The total Tinetti scale (0 to 26) consists of gait (0 to 12) and balance (0 to 16) scales and is based on a variety of items scored as 2 or 3 points per item. The gait scale scores ignition, step mechanics, arm swing, turning, and gait coordination. The balance scale scores the components of static stance and balance as well as transfers between seated and standing. Intact natural gait and balance receive the highest scores.

Statistical Analysis

Mean and SD were determined for continuous variables. Frequency and percentage of subjects showing a characteristic were determined for categorical variables. The values for FA in the genu and splenium of the corpus callosum (FA-GCC and FA-SCC) and WMH volume were evaluated as tertiles. Univariate linear regression analysis was used to determine the association between independent variables (demographic, clinical characteristics, and DTI measures) and the dependent variables (Tinetti gait, balance, and total scores). Stepwise regression analyses were performed to determine which demographic, clinical, and DTI variables independently were associated with Tinetti scores. Variables with univariate probability values $<0.05$ were considered as candidate variables in the stepwise algorithm. A probability value of $<0.05$ was considered significant. All statistical analyses were performed using SAS 9.1 (Cary, NC).
### Table 1. Demographic, Clinical, and Imaging Characteristics of Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Subjects</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>173</td>
<td>72.83±7.72</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>173</td>
<td>129 (74.57)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>172</td>
<td>145 (84.30%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>167</td>
<td>51 (30.54%)</td>
</tr>
<tr>
<td>MMSE score, 0–30</td>
<td>173</td>
<td>25.66±3.28</td>
</tr>
<tr>
<td>Depression Scale (Center for Epidemiologic Studies Depression Scale), 1–60</td>
<td>168</td>
<td>11.82±9.78</td>
</tr>
<tr>
<td>Stroke diagnosis by a neurologist, n (%)</td>
<td>173</td>
<td>30 (17.34%)</td>
</tr>
<tr>
<td>History of arthritis, n (%)</td>
<td>171</td>
<td>127 (74.27%)</td>
</tr>
<tr>
<td>Neuropathy diagnosis by a neurologist, n (%)</td>
<td>173</td>
<td>87 (50.29%)</td>
</tr>
<tr>
<td>Vision (no visual loss), n (%)</td>
<td>173</td>
<td>169 (97.7%)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>173</td>
<td>2 (1.16%)</td>
</tr>
<tr>
<td>Parkinson disease (%)</td>
<td>165</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>MRI infarcts (%)</td>
<td>171</td>
<td>49 (28.7)</td>
</tr>
<tr>
<td>Tinetti scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait (0–12)</td>
<td>173</td>
<td>10.21±2.41</td>
</tr>
<tr>
<td>Balance (0–16)</td>
<td></td>
<td>13.69±2.97</td>
</tr>
<tr>
<td>Total (0–28)</td>
<td></td>
<td>23.90±5.12</td>
</tr>
<tr>
<td>FA-GCC H</td>
<td>173</td>
<td>857.49±35.01</td>
</tr>
<tr>
<td>FA-GCC M</td>
<td></td>
<td>776.56±25.79</td>
</tr>
<tr>
<td>FA-GCC L</td>
<td></td>
<td>659.83±67.38</td>
</tr>
<tr>
<td>FA-SCC H</td>
<td>173</td>
<td>946.53±22.66</td>
</tr>
<tr>
<td>FA-SCC M</td>
<td></td>
<td>885.83±14.41</td>
</tr>
<tr>
<td>FA-SCC L</td>
<td></td>
<td>810.07±47.80</td>
</tr>
<tr>
<td>WMHV H</td>
<td>164</td>
<td>0.01±0.007</td>
</tr>
<tr>
<td>WMHV M</td>
<td></td>
<td>0.003±0.0007</td>
</tr>
<tr>
<td>WMHV L</td>
<td></td>
<td>0.0009±0.0004</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD for continuous variables. Data presented as no. of subjects affected (percent) for categorical variables.

FA-GCC H, M, L indicate highest, middle, and lowest tertiles of FA-GCC, respectively; FA-SCC H, M, L, highest, middle, and lowest tertiles of FA-SCC, respectively; WMHV H, M, L, highest, middle and lowest tertiles of WMHV volume, respectively.

### Results

#### Demographic, Clinical, and Imaging Characteristics of Subjects

The demographic, clinical, and imaging characteristics of the subjects are shown in Table 1.

#### Univariate Analyses of Subject Characteristics, FA-GCC, FA-SCC, and Tinetti Scores

The results of univariate analyses among subject characteristics, FA-GCC, FA-SCC, and Tinetti scores are shown in Table 2. Gait scores showed a significant association with MMSE, stroke, MRI infarcts, WMHV volume, and FA-GCC. There were no associations between MMSE, stroke, neuropathy, or depression. There was no association between FA-SCC and gait scores.

Balance scores were significantly associated with MMSE, stroke, neuropathy, MRI infarcts, WMHV volume, and FA-GCC. There was no association observed between balance scores and FA-SCC. There was no association with MMSE, stroke, neuropathy, MRI infarcts, WMHV volume, and FA-GCC.

#### Multiple Stepwise Regression Analyses of Subjects Characteristics and FA-GCC With Tinetti Scores

Multiple forward regression analyses were performed using FA-GCC and WMHV volume as tertiles. The results are shown in Table 3. Two models were created. In Model I, FA-GCC was the only imaging variable included as candidate variables. In Model II, WMHV volume and MRI infarcts were also included as additional candidate imaging variables to examine the independent association between FA-GCC and gait function.

In Model I, gait scores were independently associated with lowest tertile of FA-GCC, stroke, and MMSE. Subjects in the lowest tertile of FA-GCC had, on average, a 1.52-point lower gait score compared with those in the highest tertile of FA-GCC. Balance scores were independently associated with stroke, neuropathy, and the lowest tertile of FA-GCC. Presence of stroke and lowest tertile of FA-GCC independently...
stroke diagnosis by a neurologist

Neuropathy

Variable Imagination Characteristics With Tinetti Scores

Table 3. Multiple Forward Regression Analyses of Clinical and 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tinetti Gait</th>
<th>Tinetti Balance</th>
<th>Tinetti Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA-GCC L (compared with FA-GCC H)</td>
<td>$-1.52 \pm 0.41^\dagger$</td>
<td>$-1.60 \pm 0.53^\dagger$</td>
<td>$-3.11 \pm 0.89^\dagger$</td>
</tr>
<tr>
<td>FA-GCC M (compared with FA-GCC H)</td>
<td>$-0.007 \pm 0.41$</td>
<td>$0.05 \pm 0.52$</td>
<td>$0.05 \pm 0.88$</td>
</tr>
<tr>
<td>MMSE</td>
<td>$0.13 \pm 0.05^* \nonumber$</td>
<td>NA</td>
<td>$0.26 \pm 0.11^*$</td>
</tr>
<tr>
<td>Stroke diagnosis by a neurologist</td>
<td>$-1.18 \pm 0.45^\dagger$</td>
<td>$-1.33 \pm 0.56^*$</td>
<td>$-2.42 \pm 0.96^*$</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>NA</td>
<td>$-0.90 \pm 0.43^*$</td>
<td>NA</td>
</tr>
<tr>
<td>Model II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMHV H (compared with WMHV L)</td>
<td>$-1.46 \pm 0.44^\dagger$</td>
<td>$-1.33 \pm 0.57^*$</td>
<td>$-2.40 \pm 0.98^*$</td>
</tr>
<tr>
<td>FA-GCC L (compared with FA-GCC H)</td>
<td>$-1.17 \pm 0.45^\dagger$</td>
<td>$-1.41 \pm 0.57^*$</td>
<td>$-2.62 \pm 0.96^\dagger$</td>
</tr>
<tr>
<td>MMSE</td>
<td>$0.15 \pm 0.05^\dagger$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Stroke diagnosis by a neurologist</td>
<td>NA</td>
<td>NA</td>
<td>$-1.98 \pm 0.99^*$</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*p < 0.05.
†p < 0.01.
‡p < 0.001.

Discussion

The results of this prospective cross-sectional study show that white matter integrity in the genu of the corpus callosum determined by DTI is associated with quantitative measures of gait. This relationship was independent of other factors that affect gait and balance such as age, MMSE, depression, neuropathy, and stroke. This relationship persisted after WMH volume, a well-known imaging characteristic for gait impairment, was added in the analyses.9–11 If confirmed by further studies, white matter integrity in the genu of corpus callosum may prove to be an important marker of walking ability. We also observed that white matter integrity in the splenium of corpus callosum had no association with measures of gait.

Modulation of gait and balance needed for successful walking is largely an automatic task, but increasing attention has recently been given to the integrity of the neural network that manages mobility through the correct equilibrium of motor control and sensory inputs.6 Subcortical white matter disease has been shown to disrupt neural connections likely leading to impaired gait and balance.25

Previous studies have consistently shown that white matter disease depicted by WMH on conventional MRI is associated with gait impairment.9–11 We used DTI to determine the status of white matter integrity and assessed its relationship to gait function in the elderly. It has been shown that FA measurements from DTI can demonstrate age-related decline in white matter and correlate with cognitive decline in the elderly (our data not presented here also showed these relationships).26 Unlike conventional MRI, DTI can be used to assess individual projection, commissural, and association white matter tracts.14 Because most modern scanners have the ability to perform DTI and the analysis software is freely available on the Internet, this technique has the potential to be used in routine clinical practice to detect early white matter disease amenable to intervention.

Results of our DTI study in a community-based sample of elderly homebound individuals confirm previous observations of an association between white matter disease and gait impairment in the elderly. Our results also agree with the observations that atrophy of the corpus callosum is associated with gait impairment.15 Using the more refined white matter technique of DTI, we were further able to localize this particular white matter derangement to commissural tracts in the genu of the corpus callosum but not in the splenium. Connections between the left and right frontal cortices, especially the prefrontal and anterior frontal cortices, are dominant in the genu, whereas fibers interconnecting the occipital and parahippocampal cortices are found in the splenium.27 This clinicoanatomic correlation is consistent with the concept of the importance of integrated frontal executive function for the maintenance of gait and balance.28 Effective safe walking requires coordination between various levels of the nervous system and frontal coordination of the executive and cognitive functions. Our results are consistent with the concept that the white matter tracts carried in the genu of the corpus callosum are necessary for successful and safe gait, balance, and mobility. Our finding that white matter abnormalities in the genu lead to disturbance of gait and balance might also be expected to implicate frontal circuitry involved in executive function, language, and motor planning and would imply the need for clinical strategies to support loss of these functions in patients with gait disorders.

It is important to address 3 limitations of our study. First, we were able to sample only 6 directions for DTI due to contributed to >1-point decline each, on average, in the balance score. Finally, Tinetti total scores were independently associated with the lowest tertile of FA-GCC, stroke, and MMSE. Both the lowest tertile of FA-GCC and stroke independently contributed to a >2-point decline in Tinetti total scores, on average, compared with participants without these characteristics.

In Model II, gait scores were independently associated with MMSE, lowest tertile of FA-GCC, and highest tertile of WMH volume. Balance scores were independently associated only with lowest tertile of FA-GCC and highest tertile of WMH volume. Finally, Tinetti total scores were independently associated with stroke, lowest tertile of FA-GCC, and highest tertile of WMH volume. Both the lowest tertile of FA-GCC and highest tertile WMH volume independently contributed to >2-point decline in Tinetti total scores compared to participants without these imaging findings.
limitations of MRI hardware available. Second, according to the NAME study inclusion criteria, only those subjects living independently at home were included; consequently, our study population may have a selection bias toward healthier subjects with low prevalence of mobility impairment reducing the strength of relationship observed by us. Finally, findings reported do not characterize the components of gait affected by asymmetrical processes such as hemiplegia. Given the exchange of information between hemispheres, it would be expected that the FA would be abnormal regardless of a symmetrical or asymmetrical mechanism. Such a mechanistic analysis is important and will be a focus of further experiments.

Because gait is a complex function requiring coordination between various levels of the nervous system, future prospective studies with analyses of white matter tracts in the brain and spinal cord in addition to corpus callosum may help in improving our understanding of the pathophysiology of gait impairment and to assess if DTI measurements such as FA are able to predict falls in the elderly individuals.

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Disclosures
No conflicts of interest were disclosed.

References
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