Sensorimotor Function and Axonal Integrity in Adrenomyeloneuropathy

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Background: Gait abnormalities and sensorimotor disturbances are principal defects in adrenomyeloneuropathy (AMN). However, to our knowledge, their association with overall impairment and neuroanatomical changes has not been defined.

Objectives: To understand how sensorimotor impairments create mobility deficits and to analyze how these impairments are related to specific metrics of axonal integrity.

Design: Cross-sectional study assessing impairments, including vibration sensation, strength, spasticity, and global measures of walking and balance. Fractional anisotropy was measured to evaluate the integrity of the corresponding brainstem tracts.

Participants: Men with AMN and healthy control subjects.

Results: Individuals with sensory loss only showed minimal walking deficits. Concomitant strength and sensory loss resulted in slower walking, with abnormal knee control; increased spasticity led to an exaggerated trunk motion and a knee-flexed (crouched) posture. Hip strength was an independent predictor of walking velocity in subjects with AMN. Subjects with sensory loss only had greater sway amplitudes during standing balance testing, which did not worsen with additional impairments. There were significant associations among sway amplitude, great toe vibration sense, and dorsal column fractional anisotropy. Brainstem fractional anisotropy in AMN was significantly negatively correlated with impairment, indicating that overall tract integrity is associated with sensorimotor abnormalities in AMN.

Conclusions: Impairment measures capture specific abnormalities in walking and balance that can be used to direct rehabilitation therapy in AMN. Tract-specific magnetic resonance imaging metrics, such as fractional anisotropy (used herein to evaluate structure-function relationships), significantly reflect disease severity in AMN.

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healthy male control subjects (mean ± SD age, 35.8 ± 6.8 years) underwent the walking paradigm. For all other paradigms, 20 controls were matched to the 20 subjects with AMN by age and sex. Published control values for impairment measures were used for comparison.11,12 The control subjects had a passive range of motion that was at least 75% of the normal range. All subjects provided written informed consent in accord with the requirements of the institutional review board at The Johns Hopkins University.

### PARADIGMS

Overall AMN severity was evaluated using the Expanded Disability Status Scale (EDSS), a clinical rating scale ranging from 0 (normal) to 10 (death).13 We measured sensory, strength, and spasticity impairments, which reflect the functionality of the spinal cord and the brainstem tracts known to be impaired in AMN. Vibration sensation was quantified by vibration thresholds (the vibration amplitude necessary for sensation) in the great toe bilaterally, using the Vibratron II (Physitemp Instruments Inc, Clifton, NJ).14,15 Strength was quantified using a MicroFET2 hand-held dynamometer (MicroFET, Draper, Utah).12 To assess strength in muscle groups in which spasticity was not clinically evident, we averaged 2 maximal efforts of flexion or extension of both hips. Spasticity was quantified using the Modified Ashworth Scale (0 = normal) to 10 = death).13 We measured sensory, strength, and spasticity impairments, which reflect the functionality of the spinal cord and the brainstem tracts known to be impaired in AMN. Vibration sensation was quantified by vibration thresholds (the vibration amplitude necessary for sensation) in the great toe bilaterally, using the Vibratron II (Physitemp Instruments Inc, Clifton, NJ).14,15 Strength was quantified using a MicroFET2 hand-held dynamometer (MicroFET, Draper, Utah).12 To assess strength in muscle groups in which spasticity was not clinically evident, we averaged 2 maximal efforts of flexion or extension of both hips. Spasticity was quantified using the Modified Ashworth Scale (0 = normal) to 10 = death).13

### SENSORIMOTOR IMPAIRMENT ANALYSIS

Subjects were categorized as having significant impairments if they met the following criteria: for vibration sensation, a threshold that was at least 75% of the normal range. All subjects provided written informed consent in accord with the requirements of the institutional review board at The Johns Hopkins University.

#### Table 1. Subjects With Adrenomyeloneuropathy

<table>
<thead>
<tr>
<th>Subject No./Age, y</th>
<th>EDSS Score</th>
<th>Assistive Device</th>
<th>Duration of Symptoms</th>
<th>Plasma C26:0 Long-chain Fatty Acids, µg/ml*</th>
<th>Mutation Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/19†</td>
<td>0</td>
<td>No</td>
<td>None</td>
<td>1.09</td>
<td>ND</td>
</tr>
<tr>
<td>2/19†</td>
<td>1.0</td>
<td>No</td>
<td>None</td>
<td>0.87</td>
<td>I637N</td>
</tr>
<tr>
<td>3/41†</td>
<td>1.5</td>
<td>No</td>
<td>12 y</td>
<td>1.15</td>
<td>ND</td>
</tr>
<tr>
<td>4/38†</td>
<td>2.0</td>
<td>No</td>
<td>5 y</td>
<td>1.08</td>
<td>R464X</td>
</tr>
<tr>
<td>5/59†</td>
<td>2.0</td>
<td>No</td>
<td>21 y, 1 mo</td>
<td>1.42</td>
<td>G1166A</td>
</tr>
<tr>
<td>6/32</td>
<td>2.0</td>
<td>No</td>
<td>5 y, 10 mo</td>
<td>0.86</td>
<td>R464X</td>
</tr>
<tr>
<td>7/38†</td>
<td>3.5</td>
<td>No</td>
<td>4 y, 4 mo</td>
<td>1.07</td>
<td>ND</td>
</tr>
<tr>
<td>8/37†</td>
<td>3.5</td>
<td>No</td>
<td>10 y</td>
<td>0.85</td>
<td>Insertion NT1639 in C</td>
</tr>
<tr>
<td>9/26</td>
<td>3.5</td>
<td>Cane</td>
<td>7 y, 5 mo</td>
<td>1.57</td>
<td>ND</td>
</tr>
<tr>
<td>10/35†</td>
<td>4.0</td>
<td>Cane</td>
<td>5 y</td>
<td>0.97</td>
<td>ND</td>
</tr>
<tr>
<td>11/24</td>
<td>4.0</td>
<td>No</td>
<td>2 y, 6 mo</td>
<td>0.70</td>
<td>Deletion exon 3-5</td>
</tr>
<tr>
<td>12/25</td>
<td>4.5</td>
<td>No</td>
<td>2 y</td>
<td>0.81</td>
<td>C482A</td>
</tr>
<tr>
<td>13/38</td>
<td>6.0</td>
<td>No</td>
<td>8 y</td>
<td>0.95</td>
<td>ND</td>
</tr>
<tr>
<td>14/44</td>
<td>6.0</td>
<td>Cane</td>
<td>7 y</td>
<td>0.75</td>
<td>ND</td>
</tr>
<tr>
<td>15/33</td>
<td>6.0</td>
<td>Cane</td>
<td>4 y, 2 mo</td>
<td>1.44</td>
<td>E360G</td>
</tr>
<tr>
<td>16/30†</td>
<td>6.0</td>
<td>Cane</td>
<td>10 y, 9 mo</td>
<td>1.66</td>
<td>ND</td>
</tr>
<tr>
<td>17/25</td>
<td>6.0</td>
<td>Cane</td>
<td>4 y, 5 mo</td>
<td>0.93</td>
<td>ND</td>
</tr>
<tr>
<td>18/24</td>
<td>6.0</td>
<td>Cane</td>
<td>2 y</td>
<td>0.71</td>
<td>ND</td>
</tr>
<tr>
<td>19/39†</td>
<td>6.0</td>
<td>2 Canes</td>
<td>20 y</td>
<td>0.82</td>
<td>Deletion exon 6-10</td>
</tr>
<tr>
<td>20/60†</td>
<td>7.0</td>
<td>Walker</td>
<td>8 y</td>
<td>0.71</td>
<td>ND</td>
</tr>
</tbody>
</table>

#### Abbreviations: EDSS, Expanded Disability Status Scale; ND, not done.
*Normal plasma C26:0 = 0.023 ± 0.09 (SD).
†Evaluated with diffusion tensor imaging.

#### DT IMAGING ACQUISITION

We used DT imaging data from 6 age- and sex-matched control subjects participating in anatomical studies in the Human Brain Project (available at: http://cmrm.med.jhmi.edu). The scanning protocol was identical for all subjects. We used a 1.5-T magnetic resonance imaging system (Gyroscan NT; Philips Medical Systems, Best, the Netherlands). Data were acquired using a spin-echo single-shot echoplanar imaging sequence (SENSE reduction factor, 2).11,12 Other parameters included a 96 × 96–pixel matrix, reconstructed to 256 × 256 pixels, and a 240 × 240-mm field of view. At least 50 transverse 2.5-mm sections (parallel to

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the anterior commissure–posterior commissure) were acquired with 30 gradient orientations ($b$ [the diffusion weight] = 700 mm/s²). Five images with minimal diffusion weighting ($b$ = 33 mm/s²) were also acquired. Each acquisition was repeated 3 times, and these data were averaged for further analysis.

**DT IMAGING ANALYSIS**

The DT imaging data sets were processed using DTIStudio. Figure 1 shows typical DT imaging color-coded maps and corresponding FA maps for a subject with AMN and for a control subject. The regions of interest were manually selected bilaterally in the DC-ML system and in the CST in the lower brainstem sections. We averaged the FA from the DC-ML system (Dorsal Column Medial Lemniscus (DC-ML) system, 0.447; control subject: CST, 0.577; and DC-ML system, 0.460. Blue indicates superoinferior orientation; green, anteroposterior orientation; red, laterolateral orientation; V, fourth ventricle; and MCP, middle cerebellar peduncle.

Tests and nonparametric trend tests across ordered groups were performed to compare FA estimates across AMN subgroups. Spearman rank correlation was used to evaluate impairments and FA estimates. To avoid bias, investigators were blinded to the sensorimotor impairment and DT imaging results.

**RESULTS**

Test-retest reliability ICs for each impairment measure were high (vibration sensation, 0.95; strength, 0.93; spasticity, 0.95; and standing balance, 0.88). There were no significant correlations between impairment measures or with results of the very long–chain fatty acids assay or the mutation analysis. Eighteen of 20 subjects with AMN fit into 1 of 4 subgroups (no loss, SL, SSL, and SSLS). No subject had loss of strength only or spasticity only. Two subjects did not fit into the AMN subgroups: subject 9 in Table 1 was the only subject with sensory loss, spasticity, and normal hip strength, and subject 14 was not evaluated for spasticity.

**Figure 2** shows data for the 3 impairment measures among the subjects with AMN. Sensory thresholds in the great toes were severely impaired (higher) in 18 of 20 subjects with AMN, with no clear pattern across EDSS scores. Many of the subjects had poorer
(lower) strength measures in the hip flexor muscles compared with normative values; this was particularly true for the subjects with higher (more impaired) EDSS scores. Spasticity was substantial in 15 of 20 subjects with AMN; most subjects with spasticity tended to have high EDSS scores ($P = .47$). There was considerable variation among the 3 impairment measures for subjects with the same EDSS score (eg, subjects with an EDSS score of 6). The impairment measure data given in Table 2 demonstrate the magnitude of the sensorimotor loss.

Data in Figure 3 suggest that basic gait characteristics (eg, walking velocity) are affected more by strength and less by vibration sensation and spasticity. The kinematic data plotted in Figure 4 show that the AMN subgroups had different patterns of joint movement during walking. Subject 11 in the SL subgroup (Table 1 and Figure 4B) had a pattern of joint movement that was similar to that of the control (Figure 4A). Subject 20 in the SSL subgroup (Table 1 and Figure 4C) walked slowly, minimally flexed his knees during the swing phase, and had reduced ankle motion. Subject 17 in the SSLS subgroup (Table 1 and Figure 4D) had a similar pattern, although the knees were held fixed in slight flexion throughout his stride.

In Figure 4E, the data show a significant effect of AMN subgroup on knee joint excursion and on trunk anteroposterior excursion. The SL subgroup had only slight walking deficits (ankle excursion, $P = .69$; knee excursion, $P = .47$; hip excursion, $P = .12$; and trunk anteroposterior excursion, $P = .26$); the SSL subgroup walked slowly, with short steps, and had a marked change in the pattern of joint motions, particularly at the knee. The SSL subgroup walked at a similar slow speed but had additional changes in the pattern of joint motions, including increased trunk motion and a knee-flexed (crouched) posture.

We also investigated how different impairments affect walking velocity, because this has important functional significance. Hierarchical regression analysis, among all of the subjects with AMN, showed that hip strength predicted the highest percentage of the variance in walking velocity ($86\%, P < .001$), spasticity predicted a lower percentage ($13\%, P = .11$), and vibration sensation predicted the lowest percentage ($0.4\%, P = .87$).

**STANDING BALANCE**

Overall, the subjects with AMN had significantly increased sway amplitudes compared with the controls. As

### Table 2. Impairment Measure Data*

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Vibration Sensation Threshold, Great Toe, µm</th>
<th>Strength, Hip Flexion, lb</th>
<th>Spasticity Threshold, Ankle†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with AMN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td>2</td>
<td>$1.8 \pm 0.5$</td>
<td>$46.9 \pm 6.8$</td>
<td>$0$</td>
</tr>
<tr>
<td>SL</td>
<td>7</td>
<td>$46.6 \pm 6.6$</td>
<td>$46.2 \pm 3.2$</td>
<td>$1.1 \pm 0.4$</td>
</tr>
<tr>
<td>SSL</td>
<td>5</td>
<td>$58.9 \pm 26.9$</td>
<td>$17.9 \pm 7.6$</td>
<td>$1.7 \pm 0.7$</td>
</tr>
<tr>
<td>SSLS</td>
<td>4</td>
<td>$84.7 \pm 10.9$</td>
<td>$13.5 \pm 4.4$</td>
<td>$3.6 \pm 0.2$</td>
</tr>
<tr>
<td>Normative control values</td>
<td>...</td>
<td>$5.32^{10}$</td>
<td>$46.1 \pm 6.3$</td>
<td>$0$</td>
</tr>
</tbody>
</table>

Abbreviations: AMN, adrenomyeloneuropathy; NL, no significant mobility deficits; SL, sensory loss; SSL, sensory and strength loss; SSLS, sensory and strength loss with spasticity.

*Data are given as mean ± SE unless otherwise indicated.

†On the Modified Ashworth Scale, which ranges from 0 to 5.
seen in Figure 5A, the mean ± SD sway amplitude for the controls (4.64 ± 1.50 mm) was significantly lower than that for the subjects with AMN (8.49 ± 2.86 mm) (P < .05). All of the AMN subgroups had significantly greater sway amplitudes relative to those of the controls; there were no significant differences in sway amplitudes among the AMN subgroups (Figure 5B). Sway amplitude was correlated with sensory loss (r = 0.65, P < .05).

**BRAINSTEM FA AND SENSORIMOTOR IMPAIRMENTS**

We found significant relationships among DC-ML system FA, vibration sensation, and sway amplitude. Dorsal column–medial lemniscus system FA was significantly reduced in patients who did not sense the maximal vibration of 200 µm in the great toe vs those who did (P = .05).
Dorsal column–medial lemniscus system FA was significantly correlated with sway amplitude ($r = -0.7, P < .01$). Fractional anisotropy was lowest (more abnormal) in the CST than in the DC-ML system. For example, the subject with AMN in Figure 1 had CST atrophy, with no obvious DC-ML system abnormality. Overall strength and walking velocity had less robust associations with CST FA ($r = 0.35, P = .27$; and $r = 0.44, P = .17$; respectively).

Using the brainstem FA for further comparisons, our data showed significant differences between the subjects with AMN and the controls ($P < .001$) and a strong correlation between brainstem FA and EDSS scores ($r = -0.78, P < .01$). Among the 4 AMN subgroups, data showed a significant progressive rank correlation ($r = -0.69, P = .01$), indicating that overall corticospinal tract function is associated with impairment-based stratification among subjects with AMN. Differences in FA data across the AMN subgroups (Table 3) show a significant reduction of FA from the SL subgroup to the SSLS subgroup ($P < .05$), suggesting greater reduction in brainstem FA with increased impairments.

**Table 3. Fractional Anisotropy Data**

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Brainstem</th>
<th>DC-ML System</th>
<th>CST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with AMN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td>2</td>
<td>0.474 ± 0.027</td>
<td>0.518 ± 0.027</td>
<td>0.431 ± 0.027</td>
</tr>
<tr>
<td>SL</td>
<td>4</td>
<td>0.429 ± 0.012</td>
<td>0.486 ± 0.020</td>
<td>0.372 ± 0.008</td>
</tr>
<tr>
<td>SSL</td>
<td>3</td>
<td>0.401 ± 0.023</td>
<td>0.430 ± 0.019</td>
<td>0.371 ± 0.018</td>
</tr>
<tr>
<td>SSLS</td>
<td>2</td>
<td>0.392 ± 0.010</td>
<td>0.418 ± 0.040</td>
<td>0.366 ± 0.020</td>
</tr>
<tr>
<td>Control subjects</td>
<td>6</td>
<td>0.528 ± 0.018</td>
<td>0.516 ± 0.032</td>
<td>0.540 ± 0.028</td>
</tr>
</tbody>
</table>

Abbreviations: AMN, adrenomyeloneuropathy; CST, corticospinal tract; DC-ML, dorsal column–medial lemniscus; NL, no significant mobility deficits; SL, sensory loss; SSL, sensory and strength loss; SSLS, sensory and strength loss with spasticity.

*Data are given as mean ± SE.

Our data show graded abnormalities in impairment measures, which may be reflective of the progressive nature of AMN. Analyses of specific types of sensorimotor impairments in individuals revealed subgroups of AMN severity, including the SL subgroup, the SSL subgroup, and the SSLS subgroup. We hypothesize that the AMN subgroups reflect stages of disease progression. This pattern suggests that the neuropathologic features of AMN may affect DC pathways before the CST.

Results of previous studies showed that there are often systematic changes in walking patterns associated with different neuropathologic conditions. Our results indicate that subjects in the SSL subgroup had reduced flexion at the knee during the swing phase. Reduced motion across all joints would normally be expected in slower walking, our finding of reduced knee flexion only during the swing phase suggests that it is specifically related to the impairments of AMN. Hip flexion motion is an important contributor to knee flexion during the early swing phase through biomechanical coupling, via a passive pendulum-like action. Computer simulations have shown that weakened hip flexors can dramatically affect knee velocities and cause reduced knee flexion during the swing phase. We suspect that this pattern of knee motion was a byproduct of the marked hip weakness seen in our subjects with AMN.

Subjects in the SSLS subgroup had basic gait abnormalities that were almost identical to those of subjects in the SSL subgroup. The presence of spasticity changed the pattern of trunk and knee joint motion. The SSLS subgroup used increased trunk flexion or extension during walking, possibly to help advance the legs. This subgroup maintained a slightly knee-flexed posture throughout the walking and balance measures, with reduced extension during stance. We presume that spasticity contributed to this crouched posture.

Eighteen of 20 subjects with AMN had increased sway amplitudes relative to the control values; however, there was no difference in sway amplitudes among the AMN subgroups. One interpretation of this is that the static standing balance task is most dependent on sensory information that is carried in the DC and on proprioception and is less affected by weakness and spasticity; this is supported by the strong correlation between vibration sensation and sway amplitude. This suggests that sensory loss in the foot contributes to poor balance; strength and spasticity are factors that are less contributory.

The FA data show evidence of impaired axonal integrity in the DC-ML system and in the CST compared with control values. The abnormalities in the CST were more severe than those in the DC-ML system. This may be due to the contribution of the ML, which is less severely affected in a distal axonopathy because it is transsynaptic. The functional and neuroimaging abnormalities described herein are consistent with the results of pathological investigations reported by Powers et al.

The abnormalities in the DC-ML system and in the CST were significantly correlated with each other and, when combined, were strongly correlated with EDSS scores and with the AMN subgroups, reflecting the anatomical basis of the functional impairments. In addition, our FA measures indicated that individuals with sensory loss only had less white matter damage compared with individuals in the SSL subgroup. This suggests that the SSL subgroup may have a pathologically advanced disease process and supports the hypothesis that sensory deficits may begin early in the course of AMN.

In summary, this is the first study, to our knowledge, to evaluate sensorimotor function and to track axonal integrity among subjects with AMN. Impairment mea-

**COMMENT**

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sures can help in directing rehabilitation therapy, and they have the potential for use in monitoring disease progression. Fractional anisotropy measures provide an excellent way to evaluate tract-specific structural integrity. Long-range follow-up studies are under way that will more completely define the associations among AMN progression, impairment measures, and axonal integrity and will assist in the evaluation of therapeutic interventions.

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REFERENCES