Impaired Eye Movements in Presymptomatic Spinocerebellar Ataxia Type 6

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**Background:** Early detection of impaired neurological function in neurodegenerative diseases may aid in understanding disease pathogenesis and timing of therapeutic trials.

**Objective:** To identify early abnormalities of ocular motor function in individuals who have the spinocerebellar ataxia type 6 (SCA6) gene (CACNA1A) but no clinical symptoms.

**Design:** Physiological techniques were used to record and analyze eye movements and postural sway.

**Patients:** Four presymptomatic and 5 ataxic patients with SCA6, genetically identified, and 10 healthy controls.

**Results:** Presymptomatic individuals had normal postural sway but definite ocular motor abnormalities. Two had a low-amplitude horizontal gaze–evoked nystagmus, 1 of whom had a significantly decreased eye velocity for upward saccades and an abnormal frequency of square-wave jerks. Another had abnormal square-wave jerks and a fourth had a reduced gain for pursuit tracking. Not all of the presymptomatic patients had the same findings, but a multivariate analysis discriminated the presymptomatic patients, as a group, from healthy controls and the ataxic patients.

**Conclusions:** Among the earliest functional deficits in SCA6 are eye movement abnormalities, including impaired saccade velocity, saccade metrics, and pursuit gain. This suggests that early functional impairments are caused by cellular dysfunction and/or loss in the posterior cerebellar vermis and flocculus. These findings might help to determine the timing of a treatment and to define variables that could be used as outcome measures for the efficacy of therapeutic trials.

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**METHODS**

**Participants**

Four presymptomatic (2 women and 2 men) and 5 ataxic (3 women and 2 men) patients with SCA6 participated. Genetic screening for the expanded CAG repeat was performed on all participants. The mean (SD) age was 32.0 (8.1) years for the presymptomatic and 51.2 (6.4) years for the affected patients. Three of the presymptomatic patients were tested on 2...
Table 1. Neurological Features of Patients With Spinocerebellar Ataxia Type 6

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Visit</th>
<th>Sex/Age, y</th>
<th>Alleles, M/P</th>
<th>Composite Score</th>
<th>Motor System Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ocular Motor</td>
</tr>
<tr>
<td>Presymptomatic Patients (n=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-3</td>
<td>1</td>
<td>M/24</td>
<td>12/22</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>75-2</td>
<td>1</td>
<td>M/35</td>
<td>21/12</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>128-1</td>
<td>1</td>
<td>F/42</td>
<td>22/11</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>129-2</td>
<td>1</td>
<td>F/27</td>
<td>12/22</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>Ataxic Patients (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-1</td>
<td>2</td>
<td>F/58</td>
<td>12/21</td>
<td>7.0</td>
<td>3.0</td>
</tr>
<tr>
<td>129-1</td>
<td>1</td>
<td>F/57</td>
<td>12/22</td>
<td>11.5</td>
<td>3.0</td>
</tr>
<tr>
<td>209-1</td>
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<td>M/44</td>
<td>13/27</td>
<td>9.5</td>
<td>3.0</td>
</tr>
<tr>
<td>209-3</td>
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<td>M/45</td>
<td>13/27</td>
<td>11.7</td>
<td>3.0</td>
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<tr>
<td>225-1</td>
<td>1</td>
<td>F/53</td>
<td>22/14</td>
<td>7.7</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviation: M/P, maternal/paternal.

a Range, 0 to 15. Scores of 5 or greater indicate moderate to severe ataxia.
b Clinical scores (ocular motor, upper/lower limb, posture, and gait): 0=normal, 3=inability to carry out task.

Results of separate visits. Ten age-matched individuals, including 3 unaffected siblings, participated as controls. All procedures were conducted with informed consent in accordance with the institutional review board at the University of Minnesota.

CLINICAL EXAMINATION

Neurological features were characterized using a standardized examination (Table 1), which is a simplified version of the International Cooperative Ataxia Rating Scale. The clinical subtests were grouped into 5 general motor systems: eye pursuit, upper limb, lower limb, posture, and gait. The scores for the tests within each of the 5 system groups were averaged, and those average scores (1 score per system group) were added to give a composite clinical score. The range for the composite score is 0 to 15, scores of 5 or greater indicating moderate to severe ataxia. All the ataxic patients in this study had composite scores greater than 5.

EYE MOVEMENT RECORDING

The horizontal and vertical components of eye movements were recorded monocularly using the magnetic search coil technique.² For saccades, the target was displaced 5°, 10°, 20°, and 39° from one side of center to the other. The saccade gain is the ratio of the saccade amplitude to stimulus amplitude, using the initial saccade directed to the target. Data in plots of saccade velocity (V) vs amplitude (A) were fitted with an exponential function: V=Vₙ × (1−exp[−A/τ]). The value of the function, Vₙ is the peak saccade velocity (degrees/s), A is the saccade amplitude (degrees), and Vₙ and τ are the optimized (fitted) parameters; Vₙ is the asymptotic saccade velocity (the saturation value) and τ is a rate constant.

For pursuit tracking, the target moved sinusoidally with a peak-to-peak amplitude of 39° and frequencies of 0.1 and 0.2 Hz. The amplitude of the sine curve fitted to the eye velocity was used for gain and phase calculations.

STATISTICAL ANALYSIS

Statistical analyses of physiological variables were performed with SYSTAT (Systat Software Inc, San Jose, California). Univariate t tests were done to compare mean values from individual patients with those from healthy controls. Differences among the groups of presymptomatic, ataxic, and control participants were examined by analysis of variance and a multivariate linear discriminant analysis.¹ The standard deviation, SD(n-1), is the square root of the unbiased estimate of the variance and SDn is the maximum likelihood estimate.

RESULTS

CLINICAL FEATURES

The presymptomatic patients had negative responses to all questions regarding early ataxic symptoms. They also had normal neurological examination results and normal postural stability (EquiTest protocol; NeuroCom International Inc, Clackamas, Oregon), except for patient 40-3, who had mildly irregular pursuits during 2 clinical examinations (3 years apart) and slight widening of the base of gait during the first examination. Patient 40-3 also had abnormal sway scores for the vestibular-dependent posturography test conditions 5 and 6 on the first visit, consistent with the clinical scores. On the second visit, the clinical stance and posturography scores were both normal. The difference between the 2 visits could reflect variability in the disease state during the presymptomatic period. In contrast, the patients with overt ataxia had mild to severe abnormalities in all clinical examination categories and very low sway scores for the vestibular-dependent conditions.

ABNORMALLY SLOW SACCADES IN SOME PRESYMPTOMATIC SCA6

Figure 1 shows the maximum velocity vs amplitude of the initial saccade to upward and downward displaced targets for individual presymptomatic and ataxic patients. The solid exponential curves indicate the
mean (SD_{n-1}) values for the fits to the data for 10 controls. For these curves, there is a single rate constant, \( \tau \), (mean across the values for controls). The saturation velocities, \( V_s \), for the curves are the mean (SD_{n-1}) values.

One of the presymptomatic patients, patient 75-2, had decreased velocities for upward saccades for both visits (\( P < .02 \), for the 20° and 39° targets) (Figure 1A). The mean velocities for each of the other 3 presymptomatic participants were not significantly decreased, though for patient 40-3, some saccades had a decreased velocity. The downward velocities (Figure 1C) for all 4 presymptomatic participants were not significantly decreased, though patient 75-2 showed a trend for a decrease.

In contrast, all the ataxic patients showed a trend or had significantly decreased velocities, especially for downward saccades (compare Figure 1C with Figure 1D). Three of the 5 ataxic patients had significantly decreased downward velocities (Figure 1D; \( P < .03 \) for the 20° and 39° targets [patient 225-1] and the 10° target [patients 209-1 and 209-3]). Two of the 5 ataxic patients had significantly decreased upward velocities (Figure 1B; \( P < .01 \) for the 39° target for patients 209-3 and 225-1).

**DYSMETRIC SACCADES IN PRESYMPTOMATIC SCA6**

Figure 2 shows the mean (SD) saccade gains for each target for each patient. Presymptomatic patient 75-2 had hypometric (gain < 1) horizontal (Figure 2A) and downward (Figure 2E) saccades on his second visit. The gains for the other presymptomatic patients were not significantly different from healthy controls (gray regions). The gains for the ataxic patients were more variable (eg, compare the error bars for vertical saccades in Figure 2D vs...
Figure 2C and Figure 2F vs Figure 2E). Also, the direction of the dysmetria was variable among the ataxic patients: hypometric in 3 patients for horizontal and/or upward saccades (Figure 2B and D) and in 1 patient for downward saccades (Figure 2F); hypermetric (gain > 1) in 2 patients for downward saccades (Figure 2F).
Square-wave jerks are small, horizontal, saccade-like movements that take the eye away from the point of fixation and, after a delay (eg, 200 milliseconds), return the eye to its original position. Square-wave jerks were identified in all 4 presymptomatic and all 5 ataxic patients (Table 2). Within the presymptomatic group, patients 75-2 and 129-2 had higher square-wave jerk amplitudes ($P<.03$) and patients 40-3 and 75-2 had higher values for the instantaneous frequency ($P<.03$). Within the ataxic group, patients 129-1 and 209-3 had an increased frequency ($P<.001$) and amplitude ($P<.02$) and patient 129-1 had a high velocity ($P<.02$).

**GAIN OF SINUSOIDAL PURSUIT TRACKING IN THE PRESYMPTOMATIC STATE**

Figure 3 shows the pursuit gain for the presymptomatic and ataxic patients with spinocerebellar ataxia type 6. The gray regions include mean (SD) for the healthy controls. * Indicates significant difference from controls ($P<.01$).
(P < .01) and 2 others showed a trend for a reduced gain at both 0.1 Hz and 0.2 Hz for upward pursuit. In contrast, all of the ataxic patients had reduced gains (P ≤ 0.01). Vertical pursuit was impaired more than horizontal, downward more than upward. One ataxic individual, patient 225-1, had a normal gain for downward pursuit but an abnormal gain for horizontal and upward pursuit. Another ataxic individual, patient 209-1, had a normal gain for upward pursuit at 0.1 Hz but abnormal gains for all other conditions. There were no significant differences between the 2 frequencies for the group of ataxic patients, though there was a trend for lower gains at the higher frequency for horizontal pursuit.

MULTIVARIATE ANALYSIS DISCRIMINATING PRESYMPTOMATIC FROM ATAXIC PATIENTS AND HEALTHY CONTROLS

A multivariate discriminant analysis was undertaken to identify a pattern of physiological differences among 3 classification groups: the 4 presymptomatic patients, the 5 ataxic patients, and 7 of the controls who had a complete set of data for the multivariate analysis. Twelve ocular motor variables were used for the initial definition of 2 independent statistical factors. The final result showed that 10 of the variables made a significant contribution: saccade velocity (horizontal and down with the 39° target), saccade gain (horizontal and up for the 39° target), pursuit gain (horizontal and up with the 39° target at 0.2 Hz), and square-wave jerk variables (average frequency, amplitude, velocity, and duration). The standardized variables with the largest coefficients were square-wave jerk amplitude and velocity, horizontal pursuit gain, and horizontal saccade gain. Figure 4 shows the 90% confidence ellipses, which are separated from each other. There was 100% classification among the 3 groups. The Jack-knifed classification matrix, an approximate cross-validation, gave 94% correct classification.

COMMENT

In this study, we detected ocular motor abnormalities, including impaired saccade velocity, pursuit tracking, and gaze stabilization in 4 patients who possessed a repeat expansion in the SCA6 gene but had not yet developed symptoms or gross gait abnormalities. These findings are qualitatively similar to those from our recent study documenting interictal abnormalities in episodic ataxia type 2, though the molecular mechanisms affecting Purkinje cells are ostensibly different between these 2 calcium channel disorders.

DECREASE OF SACCADIC VELOCITY AND GAIN

Slowing of horizontal saccades has been reported in the presymptomatic or early symptomatic stages in SCA1 and SCA7. As the disease progresses, saccadic slowing is prominent in SCA1 and SCA2, and there is involvement of pontine neurons. Also, there can be slowing in other diseases with cerebellar but not pontine involvement.

Although slowing of saccades is not a prominent feature, it has been found in symptomatic SCA6 patients. This is consistent with our neuropathologic studies of 4 SCA6 patients. There was extensive Purkinje cell loss in the cerebellar vermis and flocculus and gliosis in the vestibular and fastigial nuclei, whereas the pontine nuclei were minimally affected. In the present study, 1 of 4 presymptomatic patients showed a significant slowing of upward saccades.

Abnormal saccadic gains were found in 2 of our presymptomatic patients. The saccades were hypometric in one and hypermetric in another. Among our ataxic patients, 4 of 5 had dysmetric saccades (horizontal and/or vertical). This is greater than that reported by Buttner et al, who found saccadic hypermetria in 40% of their ataxic SCA6 patients. However, in the latter case, only horizontal saccades were evaluated. The dysmetria could be caused by a pulse-step mismatch in the saccadic command, possibly owing to an impairment of the posterior vermis (lobules VI and VII).

DECREASE IN PURSUIT GAIN

Among the 4 presymptomatic patients, 1 had a significant decrease in upward pursuit gain but had normal pursuit in other directions. Also, 2 of the other presymptomatic participants showed a trend for a decrease in upward pursuit gain. All 5 ataxic patients had decreased gains for both horizontal and vertical pursuit. Similar findings for SCA6 were reported by Buttner et al in 5 of 5 patients (disease duration, 5-30 years) for horizontal pursuit and by Takeichi et al in 4 of 5 patients (disease duration, 5-18 years) for both horizontal and vertical pursuit. The cerebellar flocculus, ventral paraflocculus, and posterior vermis are important for controlling pursuit eye movements. Studies of pursuit-vestibular interactions and short-term vestibular ocular reflex adaptation could be explored in presymptomatic SCA6 to determine
whether these cerebellar regions are differentially affected early in the disease process.

This study, using a cohort of presymptomatic SCA6 patients, demonstrates that early functional abnormalities in SCA6 consist of saccade and pursuit eye movement abnormalities. These deficits localize to the cerebellar vermis and flocculus and possibly also to the associated vestibular and fastigial nuclei, which are among those regions of the brain in which overt cell loss or gliosis is found in postmortem studies of SCA6 patients. That the early ocular motor manifestations of the underlying pathophysiology were not uniformly manifested across all presymptomatic patients, requiring a multivariate analysis to discriminate the group from controls, implies that a very early stage in the development of SCA6 was identified.

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REFERENCES