Oculomotor Phenotypes in Autosomal Dominant Ataxias

Ned Buttner, MD, PhD; Daniel Geschwind, MD, PhD; Joanna C. Jen, MD, PhD; Susan Perlman, MD; Stefan M. Pulst, MD; Robert W. Baloh, MD

Objective: To quantify the oculomotor features of the common spinocerebellar ataxia (SCA) syndromes.

Setting: University ataxia clinic.

Patients: Twenty probands with documented SCA mutations.

Methods: Electro-oculographic recordings of sac- cadic, smooth pursuit, optokinetic, vestibular, and visual-vestibular eye movements.

Results: Distinct phenotype and genotype patterns were identified with modest overlap between patterns. Slowing of saccade peak velocities occurred only in SCA1 and SCA2, being present in 100% of patients with SCA2. Impaired vestibulo-ocular reflex gain occurred with SCA3 only. Patients with SCA6 had prominent deficits in smooth tracking but normal saccade velocities and vestibulo-ocular reflex gain.

Conclusions: The oculomotor findings are consistent with pure cerebellar involvement in SCA6, pontine involvement in SCA1 and SCA2, and vestibular nerve or nuclei involvement in SCA3. These phenotypes can be useful for clinical diagnosis and for investigating the mechanism of system specificity with the SCA syndromes.

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Catastrophically, the autosomal dominant cerebellar ataxias (ADCA) has long been a source of confusion and controversy. Harding1 separated this collection of hereditary, late-onset, cerebellodegenerative disorders into types I through III. The most common type, ADCA I, presents with a range of findings including ataxia, pyramidal and extrapyramidal signs, and ophthalmoplegia. ADCA II is similar but also includes retinal degeneration, while ADCA III involves relatively pure cerebellar signs. The advent of molecular genetics has shown this classification to be genetically heterogeneous, composed of a variety of distinct spinocerebellar ataxias (SCAs).2 SCAs 1 through 4 are forms of ADCA I, SCA5 and SCA6 are forms of ADCA III, and SCA7 so far is the only form of ADCA II. The genes for SCA1, SCA2, SCA3/Machado-Joseph disease (MJD), SCA6, and SCA7 have been cloned and found to contain expanded CAG triplet repeats.3-5 The genes for SCA4 and SCA5 have been linked to chromosomes 16 and 11, respectively, but have not been cloned.6

Most SCAs share properties typical of the CAG-repeat disorders.2,3 The size range of the repeat expansion for each is roughly similar, with less than about 30 repeats being asymptomatic and more than about 40 being symptomatic. The size of the repeat correlates with disease severity and age at onset.1 Repeat expansion constitutes the molecular basis of anticipation, which typically occurs with paternal transmission. SCA6 is the lone exception to these rules, with a smaller, stable repeat expansion thought possibly to cause a loss of function or dominant negative effect.5,6
PATIENTS AND METHODS

PATIENTS

We performed electro-oculography in 20 probands with diagnoses of SCA1, SCA2, SCA3/MJD, or SCA6. Most have been followed up on a regular basis in the ataxia clinic at the University of California, Los Angeles, Neurological Services for many years. All had clinically obvious disease of duration ranging from 2 to 30 years (Table 1).

MOLECULAR GENETIC ANALYSIS

DNA was isolated from peripheral leukocytes or lymphoblastoid cell lines as previously described. The SCA1 and SCA3/MJD alleles were amplified and analyzed on agarose and acrylamide gels by standard methods. For SCA3/MJD, the following primer pairs were used: MJDS2 and MJDB (5'-GTAACTTGCTCCTTAAATCC-3'). For SCA2 allele analysis, primers SCA2-A (5'-CAGCCCTCACCATGTCG-3') and SCA2-B (5'-CGGGCTTGGGACATTGGG-3') were used to amplify the SCA2 repeat.11

For SCA6, primers F1 and R110,12 were added to 20 to 40 ng of human genomic DNA with standard buffer and nucleotide concentrations, in a final volume of 20 µL. After an initial 5-minute denaturation at 95°C, 35 cycles of 95°C denaturation (90 seconds), 62°C annealing (30 seconds), and 72°C extension (60 seconds), followed by a final extension of 72°C for 5 minutes were performed. Expanded alleles were reamplified with the use of phosphorous expanded alleles were used to amplify the SCA6 repeat.10

EYE MOVEMENT RECORDINGS

Direct-current electro-oculogram recordings were performed in accordance with established protocols.10,12 Briefly, surface electrodes were placed at the inner and outer canthi of each eye for recording horizontal eye movements. Vertical nystagmus and blink artifact were monitored with electrodes attached above the eyebrow and below the lower lid. Calibration was performed before each subtest by having the patient look at targets in primary position and at 13° horizontally. The recording signal was amplified and filtered (cutoff frequency at 42 Hz, −3 dB), then digitized for online analysis (sampling rate, 200 Hz).

To monitor saccades, smooth pursuit, spontaneous and gaze-evoked nystagmus, and fixation instability, we asked the subject to fixate a red laser dot projected on a white screen. Horizontal saccades were induced by moving the laser dot in a stepwise pattern with pseudorandom amplitudes (3°-36°) and interstep intervals (0.5-2.5 seconds). Horizontal smooth pursuit was induced by moving the laser dot sinusoidally at frequencies of 0.1, 0.2, and 0.4 Hz (peak velocities of 11.3°/s, 22.6°/s, and 45.2°/s, respectively). Spontaneous nystagmus occurred in the primary position, while gaze-evoked nystagmus occurred on 30° horizontal or vertical gaze deviation. Rebound nystagmus was induced by saccades back to the primary position after a sustained gaze deviation, and always beat in a direction opposite to that of the preceding gaze deviation.11 Fixation instability, such as square-wave jerks, was examined with eyes in the primary position for 30-second epochs.

Horizontal optokinetic nystagmus (OKN) was obtained with subjects seated in the center of a drum (diameter, 1.3 m) made of heavy black cloth with 30 wide vertical white stripes placed at 15.6° intervals. Patients were asked to watch the stripes passing by without following them to the periphery. Sinusoidal rotation of the drum at 0.05 Hz (peak velocity, 60°/s) stimulated the entire visual field. The vestibulo-ocular reflex (VOR) was tested with passive sinusoidal rotation of the subject at 0.05 and 0.4 Hz (peak velocity, 60°/s and 30°/s, respectively). Both VOR tests were performed in darkness with the subject’s eyes open. Visual vestibular interaction was tested in 2 ways. First, the visual VOR was tested by rotating the subject in the light with the optokinetic drum stationary. Second, ability to suppress the VOR with fixation (VOR-fix) was assessed by having the patient fixate a light-emitting diode that was attached to the sinusoidally rotating chair (0.05 Hz, 60°/s).10,11 Informed consent was given by all patients.

EYE MOVEMENT DATA ANALYSIS

The methods for our online computer data analysis have been reported previously.10,12 Briefly, eye position signals were differentiated, and saccades were identified on the basis of their characteristic velocity profile. Peak velocity was averaged for saccade amplitudes of 10°, 20°, and 30° (bin width, ±2°). Saccade latency (time from target displacement to eye movement) and saccade accuracy ([saccade amplitude/target amplitude] × 100) were determined for each identified saccade. We then calculated the average saccade latency and the number of hypermetric saccades (>100% accuracy) for the entire test.

Gain measurements of VOR, OKN, and smooth pursuit were computed as follows. The fast components were removed, and the resulting gaps in the slow eye velocity record were filled by connecting the points at each end of a missing segment with a quadratic regression line. A fast Fourier analysis was then performed, giving the amplitude of the fundamental and first 3 harmonics. The amplitude of the fundamental was then compared with stimulus velocity for computation of gain. Normative data have been previously reported.10

Patient with SCA1, SCA3, and SCA6 examined. Three patients with SCA2 did not have gaze-evoked nystagmus, probably because they could not generate corrective fast components. Rebound and downbeat nystagmus were more specific. Rebound nystagmus was a prominent feature of SCA3, occurring in 100% (7/7) of patients. In comparison, rebound nystagmus was observed in 40% (2/5) of the patients with SCA6, 33% (1/3) of the patients with SCA1, and none of the patients with SCA2. Spontaneous downbeat nystagmus was even more specific, occurring in 60% (3/5) of the patients with SCA6 but in none of the other groups.

Square-wave jerks were the only saccadic intrusions identified. They occurred in 43% (3/7) of patients with SCA3, 33% (1/3) of patients with SCA1, and 20% (1/5) of patients with SCA2. Ocular flutter was not seen.

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SACCADES

Peak saccade velocity was depressed in 100% (5/5) of the patients with SCA2, but in none of those with SCA3 or SCA6 (Table 1). One of 3 patients with SCA1 had slow saccades. Figure 1 illustrates the dissociation between involvement of the fast eye-movement system in SCA2 (patient 2.4 from Table 1) vs SCA3 (patient 3.2 from Table 1). The eye-movement recording on the left shows profound impairment of saccade velocity in SCA2; here the patient is unable to generate saccade velocities greater than 100°/s at a wide range of target amplitudes.

Prolonged saccade latencies were common in SCA1 and SCA2 but did not occur in SCA6 (Table 1). Saccade hypermetria was most common in SCA3, occurring in 86% (6/7) of the patients. However, saccade hypermetria occurred in all groups: 67% (2/3) of patients with SCA1, 40% (2/5) of those with SCA2, and 40% (2/5) of those with SCA6.

SMOOTH PURSUIT, OKN, AND FIXATION SUPPRESSION OF VOR

Smooth pursuit was depressed in all 4 groups, but SCA6 was affected most severely. Pursuit data in SCA1 and SCA2 may be artificially high, because the decreased saccade velocities seen in these disorders can lead to contamination of the smooth-pursuit record by slow fast phases. As described in the "Patients and Methods" section above, saccades are identified and removed from the pursuit record on the basis of their characteristic velocity profile with a threshold for computer detection. When saccade velocity drops below this threshold, contamination of the pursuit record by slow catch-up saccades aberrantly elevates the smooth-pursuit gain. Nevertheless, patients with SCA6 had a more severe pursuit deficit than any other group. Of the patients with SCA6, 100% (5/5) displayed decreased smooth-pursuit gain, while a number of patients from other groups demonstrated normal pursuit without slow saccades (Table 1). In concert with decreased smooth-pursuit gain, OKN gain and VOR-fix gain were each noted to be impaired in all patients with SCA6.

VESTIBULO-OCULAR REFLEX

The VOR gain was normal in patients with SCA1, SCA2, and SCA6 but decreased in patients with SCA3. Of the SCA3 group, 57% (4/7) were outside the normal range, and another 29% (2/7) were in the low normal range. Three of 5 patients with SCA2 could not produce corrective fast components so that their eyes became pinned during large-amplitude (191°), low-frequency (0.05 Hz) rotation (Table 1). However, each of these had normal VOR gain when tested with small-amplitude (12°), higher-frequency (0.4 Hz) rotation where they did not require corrective fast components.

COMBINED RESULTS

The combination of saccade, pursuit, and VOR data dissociated the SCAs into relatively distinct phenotypic groups.
SCA1 and SCA2 had involvement of the fast eye movement system with decreased saccade velocity and/or saccade latency in conjunction with normal VOR gain and mild to moderately decreased pursuit. SCA3 showed a decrease in VOR gain in conjunction with normal saccades and mild to moderately decreased pursuit. SCA6 had profound abnormalities of smooth pursuit, OKN, and VOR-fix gains in conjunction with normal saccades and normal VOR gain.

Our sample size was too small to reliably correlate the severity of eye movement abnormalities with disease duration or repeat length. For SCA1, patient 1.1 had the longest disease duration and also demonstrated the slowest saccades. For SCA2, the 3 patients (2.2, 2.4, and 2.5) with the slowest saccades had the longest repeat lengths. Patient 2.1 had the smallest repeat length and the longest disease duration with intermediate slowing. For SCA3, the 2 patients with the longest disease duration had the most severely depressed VOR gain. For SCA6, there was no relationship between disease duration or repeat size and the degree of impairment of smooth pursuit and OKN gain.

**Table 2. Type and Degree of Horizontal Eye Movement Abnormalities With Different SCA Syndromes**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Saccade Velocity</th>
<th>Pursuit/OKN Gain</th>
<th>VOR Gain</th>
<th>VOR-Fix Gain</th>
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</tr>
<tr>
<td>SCA6</td>
<td>Normal</td>
<td>Severe</td>
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* SCA indicates spinocerebellar ataxia; OKN, optokinetic nystagmus; VOR, vestibulo-ocular reflex; and VOR-Fix, VOR with fixation.

**Figure 1. Saccadic eye movements in patient 2.4 with spinocerebellar ataxia 2 (left) and patient 3.5 with spinocerebellar ataxia 3 (right). Horizontal monocular electro-oculogram recordings. Plots of peak velocity vs amplitude for each saccade in the random sequence (top). Dotted lines show normal range.**

**Figure 2. Combined smooth pursuit, saccade, and vestibulo-ocular reflex (VOR) data for each patient with spinocerebellar ataxia 1, 2, 3, and 6, showing separation into distinct phenotypes.**

**COMMENT**

Our findings are consistent with previous studies with a few exceptions. Numerous clinical studies have identified supranuclear ophthalmoplegia in patients with SCA3/MJD. We found normal horizontal saccade velocities in all 7 of our patients with SCA3. Burk et al reported mildly decreased horizontal saccade velocities in 30% of their 32 patients with SCA3. However, saccade velocity measurements in their patients with SCA3 were not significantly different from those in controls. How do we explain this apparent conflict between clinical observations and quantitative eye-movement data? Few details regarding the nature of the supranuclear ophthalmoplegia seen with SCA3 have been reported, but, on the basis of our clinical experience, vertical-gaze disorders are much more common than horizontal-gaze disorders in SCA3/MJD. This vertical-horizontal dissociation in eye movement involvement is common in diseases that affect the basal ganglia. Since we measured only horizontal saccades, abnormalities of vertical saccades would not be identified. Also, since supranuclear gaze disorders are reported to increase with disease duration, we probably would have identified a few cases of SCA3 with slow horizontal saccades if we had studied more patients with longer disease dura-
tion. Only one of our patients with SCA3 had had symptoms for more than 10 years. Klostermann et al reported impaired VOR responses in their patients with SCA1, yet all of our patients with SCA1 had normal VOR gain. On review of their eye movement recordings, however, the problem was impaired fast components rather than VOR slow components, similar to the problem we had with the low-frequency data in patients with SCA2. Testing with smaller-amplitude, higher-frequency stimuli would probably have shown normal VOR responses in their patients with SCA1.

It is of interest to compare SCA phenotypes with those of older diagnostic categories, such as olivopontocerebel lar atrophy and cerebellolo-olivary atrophy. Patients previously diagnosed as having olivopontocerebellar atrophy share similar oculomotor abnormalities with patients now known to carry mutations for SCA1, SCA2, and SCA3. The olivopontocerebellar atrophy phenotype included impaired saccade velocity and latency, now seen to be characteristic of SCA1 and SCA2, and included depressed VOR now seen to be characteristic of SCA3. Cerebellolo-olivary atrophy and SCA6 share the common findings of normal saccade velocity and VOR gain but severely impaired smooth pursuit, OKN, and VOR-fix gains with both downbeat and rebound nystagmus. Many patients diagnosed as having cerebellolo-olivary atrophy likely carried the expanded repeat in the repeat-dependent calcium channel now termed SCA6.10 Also of note is the similarity in oculomotor profiles of SCA3 and Friedreich ataxia. Impaired VOR, saccade dysmetria, and slow-wave jerks are common in both conditions.10

Evidence from experimental animals indicates that many of the SCA oculomotor abnormalities described above localize to the cerebellum. Virtually all patients with SCA displayed gaze-evoked nystagmus and varying degrees of involvement of the slow visual tracking system, ie, decreased smooth-pursuit gain, decreased OKN gain, and increased VOR-fix gain. These abnormalities are associated with lesions of the posterior vermis, flocculus, and paraflocculus. Rebound and downbeat nystagmus localize to the flocculus and paraflocculus as well.12 Saccade dysmetria localizes to the dorsal cerebellar vermis and fastigial nuclei.13 Abnormalities of the fast eye-movement system imply extracerebellar disorders, specifically the paramedian pontine reticular formation, to explain the decreased saccade velocities with SCA1 and SCA2. The decreased VOR gain with SCA3 suggests bilateral involvement of primary vestibular neurons (as has been reported with FA or brainstem vestibular pathways. Magnetic resonance imaging studies in patients with SCA are consistent with these localizations, showing pure cerebellar atrophy in patients with SCA6 and pontine atrophy in patients with SCA1 and SCA2.15

How CAG repeat expansion in different genes can produce system-specific abnormality is not known. The repeat expansion lies within the coding region of each SCA gene and is predicted to give rise to a polyglutamine tract.23,24 Recent reports suggest that the polyglutamine tract itself acts as a common effector mechanism leading to toxic effects.25,26 If indeed this is the case, individual proteins may guide cell-specific expression of the repeat expansion. A first step to answering the above question for the SCAs is to define the extent of system specificity and the identity of the systems affected. Here we show that relatively specific phenotypes for the SCAs can in fact be detected with quantitative eye movement testing.

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Reprints: Robert W. Baloh, MD, Department of Neurology, UCLA, Box 951769, Los Angeles, CA 90095-1769 (e-mail: rwbaloh@ucla.edu).

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