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# Clinical Evaluation of Eye Movements in Spinocerebellar Ataxias: A Prospective Multicenter Study

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## Abstract

**Background—**Ocular motor abnormalities reflect the varied neuropathology of spinocerebellar ataxias (SCAs) and may serve to clinically distinguish the different SCAs. We analyzed the various eye movement abnormalities detected prospectively at the baseline visit during a large multicenter natural history study of SCAs 1, 2, 3, and 6.

**Methods—**The data were prospectively collected from 12 centers in the United States in patients with SCAs 1, 2, 3, and 6, as part of the Clinical Research Consortium for Spinocerebellar Ataxias (NIH-CRC-SCA). Patient characteristics, ataxia rating scales, the Unified Huntington Disease Rating Scale functional examination, and clinical staging were used. Eye movement abnormalities including nystagmus, disorders of saccades and pursuit, and ophthalmoparesis were recorded, and factors influencing their occurrence were examined.

**Results—**A total of 301 patients participated in this study, including 52 patients with SCA 1, 64 with SCA 2, 117 with SCA 3, and 68 with SCA 6. Although no specific ocular motor abnormality was pathognomonic to any SCA, significant differences were noted in their occurrence among different disorders. SCA 6 was characterized by frequent occurrence of nystagmus and abnormal pursuit and rarity of slow saccades and ophthalmoparesis and SCA 2 by the frequent occurrence of

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slow saccades and infrequent nystagmus and dysmetric saccades. SCA 1 and SCA 3 subjects had a more even distribution of eye movement abnormalities.

**Conclusions—**Prospective data from a large cohort of patients with SCAs 1, 2, 3, and 6 provide statistical validation that the SCAs exhibit distinct eye movement abnormalities that are useful in identifying the genotypes. Many of the abnormalities correlate with greater disease severity measures.

Spinocerebellar ataxias (SCAs), by convention, denote a group of progressive autosomal dominant disorders that are genetically, clinically, and pathologically heterogeneous. Both cerebellar and extracerebellar involvement may occur accounting for the complex clinical picture of the SCAs (1–3). SCAs are associated with a variety of abnormalities in eye movements; some of these results from abnormalities in cerebellar control, whereas others reflect extracerebellar pathology. Previous publications have documented the type of abnormalities noted in families examined during gene identification studies, in small scale reports using eye movement recordings (4–10) and in larger patient cohorts of SCA subjects (11,12). We summarize the findings of bedside ocular motor examination performed prospectively in a large cohort of patients with SCAs 1, 2, 3, and 6 and examine factors that may influence their presence. Such data may provide clues for obtaining the appropriate diagnostic gene testing and provide information as to the neuronal subsets involved in each disorder.

## Methods

### Clinical Method

Data were collected prospectively during an NIH-funded natural history study on SCAs 1, 2, 3, and 6, conducted at 12 U.S. centers as part of the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) (13). This is one of the 19 rare disease consortia of the Rare Disease Clinical Research Network. The protocol was approved by local ethics committee at each institution, and informed consent was obtained from all participants.

Inclusion criteria were 1) DNA diagnosis of SCAs 1, 2, 3, or 6 in the study subject or his/her affected family member(s); 2) phenotype consistent with the DNA diagnosis; 3) willingness to participate in the study; and 4) age of ≥ 6 years. The exclusion criteria were 1) known recessive, X-linked or mitochondrial ataxia; 2) concomitant disorder (s) that affect Scale for Assessment and Rating of Ataxia (SARA) and other ataxia measures used in this study (e.g., additional neurological illness such as stroke or significant orthopedic disease); and 3) exclusion of SCAs 1, 2, 3, and 6 by DNA testing. At the baseline visit, a complete neurological examination was performed using preformatted case-report forms (CRFs) in which several distinct features of all neurological deficits were recorded by neurologists experienced in the field of ataxia. Eye movement examination used accepted bedside techniques (14) and included pursuit in all directions, examination of horizontal and vertical saccades for both speed and accuracy, careful examination of completeness of eye movements in all directions with urging of the patients to move eyes fully, and detection of nystagmus in primary position and eccentric gaze. The CRFs were used to record all these specific features of eye movements. Ataxia was quantified using SARA (15) and functional

status using the Unified Huntington Disease Rating Scale (UHDRS, with permission from Huntington Study Group). The mobility status was rated using a functional stage classification (16). Blood samples were collected from participants for a reanalysis and confirmation of their mutation status (Laboratory of Stefan M. Pulst, Salt Lake City, UT) and additional gene-modifier studies. The subjects were recruited during the period spanning from July 2009 to May 2012.

### Genetic Testing

In 263 patients, the size of the respective cytosine–adenine–guanine (CAG) expansion responsible for the SCA was estimated in one of the investigator's laboratory (S.M.P.). DNA was extracted using a Qiagen FlexiGene DNA Kit (Qiagen, Valencia, CA). CAG repeat lengths were determined by multiplex polymerase chain reaction followed by capillary electrophoresis with internal standards. DNAs were tested for the presence of mutant alleles in the SCAs 1, 2, 3, and 6 genes. Regenotyping and Sanger sequencing were performed for verification of repeat length on 10% of all samples. Two CEPH DNA samples (1331-02 and 1347-02) were included in every run for every marker as an additional internal sizing control. In an additional 38 patients whose samples were not available in the research laboratory, the values from commercial laboratory results were used.

### Statistical Analysis

In the analysis of demographic features, specific SCA subtypes (1, 2, 3, and 6) were compared using $\chi^2$ tests for categorical variables, analysis of variance for continuous variables, and Kruskal–Wallis for ordinal variables. The prevalence of various eye movements among the SCA subtypes was then compared with $\chi^2$ tests. To assess the significance of the number of repeats on disease onset and clinical outcome scores, regression analyses were performed. Specifically, linear regression was performed for continuous variables, but ordered logistic regression was used in the assessment of ordinal variables. Logistic regression was used to assess the relationship between number of repeat and the prevalence of various eye movements. Finally, patients with and without SCA-associated eye movement were compared using $\chi^2$ tests for categorical variables, t tests for continuous variables, and Wilcoxon–Mann–Whitney tests for nonparametric variables. *P*-values were adjusted for multiple comparisons. All statistical analyses were performed with Stata/SE 10.0 (StataCorp, College Station, TX).

## Results

A total of 301 subjects were evaluated in this study, including 52 SCA 1, 64 SCA 2, 117 SCA 3, and 68 SCA 6 patients. Demographic features of the group are shown in Table 1. Although there was a wide range of clinical severity, the mean SARA scores and functional stage in these patients reflect a moderately advanced stage of disease. In comparing patients with SCAs 1, 2, 3, and 6, no differences were identified in gender distribution, UHDRS functional examination score, and functional disease stage. However, differences were noted in all other demographic features and SARA scores.

Table 2 summarizes the ocular motor abnormalities seen in our patient cohort. There was no abnormality that was unique to any SCA, but in comparing patients with SCAs 1, 2, 3, and 6, significant differences were identified in the prevalence of each eye movement abnormality. Diplopia as a symptom was most prevalent in SCA 3 and SCA 6 and occurred in fewer than 25% of SCA 1 and SCA 2 patients. Abnormal pursuit was more common in SCA 6 and SCA 3 as was gaze-evoked nystagmus (GEN); nystagmus occurred only in 13% of SCA 2 patients. Inaccurate saccades were noted among all SCA patients, hypermetric saccades being more common than hypometric saccades except in SCA 2. Saccade velocity slowing was noted in 80% of SCA 2 patients and was least common in SCA 6 (11%).

We examined the influence of the following variables on the ocular motor abnormalities: gender, age at examination, age at onset, duration of disease, number of CAG repeats in the expanded alleles, SARA score, and mobility status as assessed using the functional staging. The results are summarized in Table 3.

## Discussion

Eye movements serve to either acquire novel visual targets on the fovea or to stabilize targets of interest on the fovea; the saccadic, pursuit, and vestibular systems, among others, are important in achieving these goals (17). Many neuronal subsets in both the cerebellum and brainstem play key roles in controlling eye movements, and it is not surprising that patients with SCA have a variety of eye movement abnormalities (18,19). This report summarizes the findings of ocular motor examination “at the bedside” performed in a prospective fashion in a large cohort of subjects with SCAs 1, 2, 3, and 6.

Horizontal GEN was a common finding in SCAs 6, 3, and 1 (in that order) and least common in SCA 2, occurring only in 13% of patients. GEN is almost universal in SCA 6 (7,20–22). The infrequency of GEN in SCA 2 has been noted in other clinical studies (11,12). Eye movement recordings have either not detected GEN in SCA 2 (10) or found it in fewer than 50% of subjects (7,20). The flocculonodular lobe is important for gaze holding, and damage to this area would explain GEN. These structures are believed to provide a positive feedback to the ocular motor “integrator” in the brainstem, important for converting the velocity signal of an eye movement to a position command. Pathology in brainstem neurons that serve as integrator of eye movements can also explain the nystagmus (23). Interestingly, Ying et al (24) found that the flocculonodular lobe was indeed atrophied in SCA 2 and suggested that gaze-holding functions may not be detected accurately at the bedside in this disease.

Inaccurate saccades were most frequent in SCA 6 and SCA 3 and least so in SCA 2; hypermetric saccades were usually much more common than hypometric saccades. Oculographic studies on more limited numbers of subjects have noted similar findings (7,8). The superior colliculus, brainstem, and cerebellum are involved in a circuitry necessary for online correction of saccade amplitude and its rapid adaptation in different behavioral conditions (17). The function of a saccade is to be simultaneously fast and accurate, especially when the stimulus is unexpected and potentially threatening. The dorsal oculomotor vermis (OMV) (lobules V–VII) and the related fastigial nuclear cells are

important for saccadic amplitude and direction; bilateral OMV lesions cause hypometric saccades, and in contrast, bilateral lesions of the fastigial nucleus result in hypermetric saccades (18). Purkinje cells in the OMV discharge before saccades and the fastigial nuclear cells fire before contraversive saccades and late during ipsiversive saccades, providing a "braking" discharge. It is interesting to note that hypermetric saccades were usually more frequent than hypometric saccades except in SCA 2, an observation that confirms the findings of Maschke et al (11). Also in SCA 2, hypometric saccades correlated with poorer functional stage of disease.

In addition to dysmetric saccades, slow saccades were documented in all SCAs, most frequently in SCA 2 and least in SCA 6. This has been reported previously, although in SCA 3 patients, eye movement recordings have suggested that saccade slowing is uncommon (7,10). The paramedian pontine reticular formation is critical for the generation of horizontal saccades, particularly the excitatory burst neurons. A specific loss of the excitatory burst neurons has been documented in a case of SCA 2 (25). In our study, the occurrence of slow saccades was correlated with many measures reflecting higher disease severity (Table 3). This suggests that the saccade generators become involved at a later stage of disease.

Ophthalmoparesis generally was less common than other ocular motor abnormalities; it was least common in SCA 6 and most common in SCA 3. Vertical ophthalmoparesis was more common than horizontal ophthalmoparesis. Other reports have noted much higher prevalence of ophthalmoplegia in SCAs 1, 2, and 3 (11,20). Even in SCA 6, these previous studies documented ophthalmoplegia ranging from 24% to 48% of cases; this was not our experience, and we believe that ophthalmoparesis of a significant nature would be incompatible with SCA 6, although some degree of ocular motor neuron loss has been found in neuropathological studies (26). Whether the decline in ocular motility has an infranuclear or supranuclear origin could not be determined in our study. Higher SARA scores and poorer functional stage correlated with ophthalmoparesis in SCA 1 and SCA 3, indicating the involvement of ocular motor neurons in later stages of disease. Diplopia was a more common symptom not only in SCA 3 but also in SCA 6, but fewer than 25% of SCA 1 and SCA 2 patients had this symptom. Among patients who complained of diplopia, horizontal or vertical ophthalmoparesis was noted least frequently in SCA 6 (4% and 14%, respectively); the respective percentages for horizontal and vertical ophthalmoparesis among patients with diplopia in the other SCAs were 31% and 39% in SCA 1, 30% and 50% in SCA 2, and 49% and 63% in SCA 3. Therefore, in addition to ophthalmoparesis, diplopia may be related to other factors such as the role of cerebellum in maintaining conjugate gaze.

Pursuit abnormalities were seen in over 70% of patients with SCA 3 and SCA 6 and in a smaller percentage of SCA 1 and SCA 2 patients. Lesions of the flocculonodular lobe are known to decrease the gain of pursuit movements. A diminished gain of pursuit has been documented by eye movement recordings in all of these SCAs (7,20–22). In SCAs 1 and 2, lower SARA scores correlated with occurrence of pursuit abnormalities. This together with the observations on saccadic velocity abnormalities noted in these diseases suggests that abnormal pursuit becomes more difficult to detect because the saccadic system becomes involved with more severe disease.

Square-wave jerks are involuntary saccades that take the eyes off the target and are followed after a normal intersaccadic interval by a corrective saccade back to the target. The topographic diagnostic value of square-wave jerks is unclear. We found that square-wave jerks (≥10 per minute) to be more prevalent in SCA 3 (23%), but also it was present in SCA 6 (17%), SCA 1 (11%), and in 5% of SCA 2 patients.

In a large clinical study of 526 subjects with SCAs 1, 2, 3, or 6, Jacobi et al (12) found a similar prevalence of abnormal pursuit and GEN as in our report; dysmetric saccades were found in a larger proportion of subjects with all SCAs in that study but were not reported as being hypermetric or hypometric. In 79 subjects with SCAs 1, 2, 3, and 6, Maschke et al (11) found similar abnormalities (11). However, the following differences were noted from our current observations: all types of ophthalmoparesis were more frequent in all SCAs; pursuit abnormalities were much more frequent in SCA 1 and SCA 2; and GEN was more frequent in SCA 1 and SCA 6.

In conclusion, clinical observations of eye movement abnormalities are useful indicators of different types of SCAs. We provide data regarding factors that influence the occurrence of these abnormalities and point to early or late involvement of neuronal populations in different SCAs. This is supported by the limited data available on the neuropathology of these SCAs (25,26). More detailed, longitudinal, and quantitative observations may further clarify these observations.

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**Table 1**

**Demographic features of patients with SCA**

| | SCA 1 (n = 52); *P* | SCA 2 (n = 64); *P* | SCA 3 (n = 117); *P* | SCA 6 (n = 68); *P* | *P* |
|---|---|---|---|---|---|
| Gender (male), n (%) | 22 (42%); 0.47 | 29 (45%); 0.78 | 58 (50%); 0.45 | 32 (47%); 0.97 | 0.84 |
| Race (white), n (%) | 49 (94%); <0.001 | 50 (78%); 0.41 | 62 (53%); <0.001 | 62 (91%); <0.001 | <0.001 |
| Age, yr | 49.6 (12.5); 0.022 | 49.3 (13.0); 0.004 | 51.0 (11.5); 0.011 | 64.5 (10.8); <0.001 | <0.001 |
| Age of onset, yr | 40.5 (11.3); 0.31 | 35.4 (11.4); <0.001 | 40.3 (11.4); 0.053 | 52.6 (9.9); <0.001 | <0.001 |
| Disease duration, yr | 9.2 (7.1); 0.041 | 13.7 (8.5); 0.003 | 10.5 (7.2); 0.16 | 12.1 (9.9); 0.38 | 0.013 |
| SARA score | 14.0 (8.6); 0.16 | 17.7 (7.2); 0.004 | 15.1 (8.9); 0.39 | 14.8 (7.4); 0.59 | 0.033 |
| UHDRS | 17.8 (6.2); 0.28 | 17.1 (6.3); 0.77 | 16.4 (6.5); 0.23 | 17.2 (5.7); 0.90 | 0.60 |
| Functional stage | 2.8 (1.3); 0.11 | 3.0 (1.2); 0.96 | 3.1 (1.3); 0.61 | 3.1 (1.3); 0.37 | 0.44 |

Values are reported as mean (SD); *P* value, unless otherwise noted. The *P*-value under each data point represents a comparison of that particular SCA against all other SCAs. These *P*-values were calculated with $\chi^2$ tests for categorical variables, *t* test for continuous variables, and Wilcoxon–Mann–Whitney test for nonparametric variables. The *P*-value in the final column represents the comparison of each individual SCA (4-group comparison). The final column *P*-value was calculated with $\chi^2$ tests for categorical variables, analysis of variance for continuous variables, and Kruskal–Wallis for nonparametric variables.

SARA, Scale for Assessment and Rating of Ataxia; SCA, spinocerebellar ataxia; UHDRS, Unified Huntington Disease Rating Scale.

**Table 2**

**Prevalence of eye movement abnormalities in patients with SCA**

| | SCA 1 (n = 56) (*P*) | SCA 2 (n = 69) (*P*) | SCA 3 (n = 119) (*P*) | SCA 6 (n = 72) (*P*) | *P*-Value Comparing All SCAs |
|---|---|---|---|---|---|
| Diplopia | 24 (0.010) | 18 (<0.001) | 61 (<0.001) | 43 (0.70) | <0.001 |
| GEN | 44 (0.067) | 13 (<0.001) | 77 (<0.001) | 78 (<0.001) | <0.001 |
| Hypermetric saccades | 41 (0.67) | 14 (<0.001) | 50 (0.042) | 51 (0.056) | <0.001 |
| Hypometric saccades | 20 (0.13) | 28 (0.81) | 34 (0.038) | 21 (0.19) | 0.17 |
| Slow saccades | 47 (0.49) | 80 (<0.001) | 40 (0.31) | 11 (<0.001) | <0.001 |
| Horizontal ophthalmoparesis | 22 (0.63) | 15 (0.22) | 35 (<0.001) | 2 (<0.001) | <0.001 |
| Vertical ophthalmoparesis | 28 (0.67) | 25 (0.46) | 47 (<0.001) | 6 (<0.001) | <0.001 |
| Abnormal smooth pursuit | 45 (0.019) | 37 (<0.001) | 70 (0.023) | 79 (0.001) | <0.001 |
| Square-wave jerks | 11 (0.14) | 5 (0.019) | 23 (0.004) | 17 (0.87) | 0.012 |

Values are reported as % (*P*). The *P*-value is a comparison of that particular SCA against all other SCAs, as calculated with a $\chi^2$ test. The final column represents the *P*-value in comparing each individual SCA, as calculated with a 4-group $\chi^2$ test.

GEN, gaze-evoked nystagmus; SCA, spinocerebellar ataxia.

## Table 3

**Factors related to various ocular motor abnormalities in patients with SCA types 1, 2, 3, and 6**

| Ocular Motor Symptom/Abnormality | Disease | Factors Reaching Significance |
|---|---|---|
| Diplopia | SCA 3 | Longer disease duration, higher SARA score, and poorer functional stage |
| Abnormal pursuit | SCA 1 | Lower SARA score |
| | SCA 2 | Lower SARA score |
| | SCA 3 | Higher age and higher age at onset |
| | SCA 6 | Shorter disease duration |
| Hypermetric saccades | SCA 1 | Higher age and higher age at onset |
| | SCA 2 | Lower SARA score and better functional stage |
| Hypometric saccades | SCA 2 | Poorer functional stage |
| Horizontal ophthalmoparesis | SCA 3 | Higher SARA score |
| Vertical ophthalmoparesis | SCA 1 | Higher SARA score and poorer functional stage |
| | SCA 3 | Higher repeats, higher SARA score, and poorer functional stage |
| Slow saccades | SCA 1 | Higher repeats, disease duration, higher SARA score, and poorer functional stage |
| | SCA 2 | Higher SARA score and poorer functional stage |
| | SCA 3 | Higher repeats, disease duration, higher SARA score, and poorer functional stage |

SARA, Scale for Assessment and Rating of Ataxia; SCA, spinocerebellar ataxia.