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SHORT REPORTS

Eye Movement Abnormalities Are Ubiquitous in the Spinocerebellar Ataxias

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Abstract

Oculomotor abnormalities are common in the spinocerebellar ataxias (SCAs). In studies of SCAs 1, 2, 3, and 6, eye movement abnormalities correlate with disease severity. Oculomotor abnormalities may be the sole motor manifestation of early and/or premanifest disease; however, not all ataxia rating scales include oculomotor assessment. We sought to identify the prevalence and characteristics of oculomotor abnormalities at first presentation in a large SCA cohort, including those in earlier stages of disease. We performed a retrospective assessment of initial clinical examinations of SCA patients followed in the Massachusetts General Hospital Ataxia Unit and assessed with the Brief Ataxia Rating Scale (BARS). One hundred thirty-four SCA patients were assessed: 17 SCA1, 13 SCA2, 55 SCA3, 2 SCA5, 22 SCA6, 11 SCA7, 9 SCA8, and 5 SCA17, mainly in the early stages of disease (67.2% stage 0–1). Oculomotor abnormalities were present on initial assessment in 94.8%, including 7/9 stage 0 and 77/81 stage 1 patients. Stage 0/1 patients had frequent saccadic intrusions, nystagmus, and hypo/hypermetric saccades. Saccadic slowing was present even in early stage SCA7 and SCA2, eventually leading to ophthalmoplegia. The burden of oculomotor abnormalities correlated with disease stage, duration, and severity, remaining highly significant even when controlling for age. The ubiquitous presence of oculomotor abnormalities in the SCAs, particularly early in the course, underscores the importance of oculomotor assessment in ataxia rating scales such as BARS. These findings highlight the potential for quantitative physiological oculomotor measures as clinical biomarkers in natural history studies and clinical trials.

Keywords Clinical neurology examination · Spinocerebellar ataxia · Ocular motility, ocular physiological phenomena

Introduction

The spinocerebellar ataxias (SCA) are rare, genetically and clinically heterogeneous autosomal dominant movement disorders that cause progressive debilitation and often lead to early death. There are currently no effective treatments. Eye movement abnormalities are common in the SCAs [1] and represent a cardinal feature of the cerebellar motor syndrome in addition to gait ataxia, appendicular dysmetria, and cerebellar dysarthria. Cerebellar oculomotor signs include square wave jerks and nystagmus in primary position, saccadic pursuits, saccadic hypermetria/hypometria, gaze-evoked direction-beating nystagmus, impairment of oculokinetic response, failure to suppress the vestibulo-ocular reflex, and slowing of saccades or pursuit, potentially leading to complete external ophthalmoplegia. Abnormal eye movements may be the sole clinical manifestation of early disease [2], help distinguish between different SCAs [1], and differentiate cerebellar from other neurodegenerative disorders [3].

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The multi-center study of the Clinical Research Consortium (CRC) for spinocerebellar ataxias [1], assessed 301 patients with SCA 1, 2, 3, and 6 in moderately advanced stages of disease. Eye movement abnormalities were highly prevalent, and while many correlated with disease severity, none was pathognomonic for any specific SCA [1]. Quantitative testing by electro-oculography [4] and video-oculography [5] have also demonstrated differences between the different SCAs. Furthermore, oculomotor abnormalities have been identified in premanifest patients on clinical examination [2] and by quantitative testing [6]. There is presently no information available regarding the frequency and type of oculomotor abnormalities in the SCAs at initial clinical visit to aid the clinician in making the diagnosis. We therefore sought to identify the prevalence and characteristics of oculomotor abnormalities in a large cohort of SCA patients at first clinical presentation to the Massachusetts General Hospital (MGH) Ataxia Unit, including patients in earlier stages of disease.

Methods

This study was approved by the MGH Human Studies Committee. We performed a retrospective chart review of all patients followed at the MGH Ataxia Unit with a genetically confirmed diagnosis of SCA between January 2000 and March 2018. Data from 9 additional subjects seen at the MGH as part of the CRC SCA natural history study were included in the analysis. Clinical examination including detailed oculomotor examination performed by ataxia specialists at the first clinical visit was assessed, on many occasions without being aware of the genetic diagnosis at the time. Ataxia severity was assessed using the Brief Ataxia Rating Scale (BARS) [7], utilizing a new half-point scale currently in development, reflecting a more nuanced approach than the current BARS score. Disease stage was defined per Klockgether et al. [8] (stage 0: no gait difficulties; stage 1: onset of gait disorder; stage 2: walking aid required; stage 3: wheelchair-bound.). All patients were assessed with the Functional Staging for Ataxia (FSA, score 0–6) [9]. Disease onset and duration were defined by patient report of symptom onset or the presence of diagnostic examination features. Statistical analysis was performed with SAS version 9.4 (SAS Institute Inc., Cary, NC). We performed descriptive statistics detailing the presence on examination of oculomotor features (abnormal movements at rest, with pursuit and saccade, saccadic slowing, and nystagmus) and assessed as a whole, and we also analyzed subgroups by genetic SCA diagnosis and by disease stage. Chi-square tests were performed for categorical variables across individual SCAs, and analysis of variance (ANOVA) for continuous variables across groups. We performed Pearson correlation coefficients to assess for correlation between the BARS oculomotor score (as a measure of the burden of oculomotor abnormalities), overall clinical disease severity (the total BARS score not including the oculomotor subscore), gait severity (BARS gait subscore) and disease duration. We performed subgroup analysis in patients with early stages of disease and short symptom duration (defined as within 3 years of symptom onset). We performed linear regression modeling to assess for possible confounders, including age at assessment because of the potential influence of age on eye movements.

The updated BARS oculomotor score describes the presence/absence of the four cardinal features of oculomotor impairment including movements at rest, saccadic pursuit, pathological gaze-evoked nystagmus, and saccadic hypermetria/hypometria. These binary conditions allow derivation of a reliable oculomotor score for clinical purposes. A half-point is scored for each of the four conditions, yielding scores ranging from 0 (normal) to 2. When eye movements are slowed, severity of slowing is rated as normal (0), mildly (0.5), moderately (1), severely slowed (1.5), or ophthalmoplegia (2). If slowing is present in addition to other features, the degree of slowing is scored—thus moderately slowed eye movements with overshoot would be scored as a 1 out of 2. Severity assessment for the other parameters is not feasible, as this can only be reliably performed by quantitative oculography. The vestibulo-ocular reflex cancellation test (VORC) is a helpful office test that we use to evaluate many of our ataxia patients. We do not use it routinely in all patients, however, and it does not constitute part of the BARS oculomotor assessment. For this reason, the VORC was not included in the present analysis.

Results

One hundred thirty-four SCA patients were assessed: 17 SCA1, 13 SCA2, 55 SCA3, 2 SCA5, 22 SCA6, 11 SCA7, 9 SCA8, and 5 SCA17. Demographic details are shown in Table 1. Most patients were seen in the early stages of disease (90/134, 67.2% stage 0–1). Oculomotor abnormalities were present in 127/134 (94.8%) of the cohort. 103/134 (76.8%) had greater than one oculomotor abnormality (mean number of eye signs 2.3 ± 1.1), with a higher burden in later stages. Even in early stages, eye movements were abnormal in 7/9 (77.8%) stage 0 patients and 77/81 (95.1%) stage 1 patients and were near-ubiquitously abnormal later, involving 30/31 stage 2 (96.8%), and 14/14 (100%) stage 3 patients.

The number of abnormal eye signs was different across the SCAs (ANOVA, $p = 0.02$). Although limited by sample size, there were also differences in oculomotor abnormalities between SCA2, 3, and 7 ($p < 0.05$ on Bonferroni correction), as shown in Table 2. Saccadic pursuit was common in our cohort and varied by SCA type ($p = 0.0003$). This likely reflected the overriding presence of slowing of both pursuit eye movements

Table 1 Demographic details of SCA cohort

Characteristic	SCA diagnosis									*p* value
	Total (*n* = 134)	SCA1 (*n* = 17)	SCA2 (*n* = 13)	SCA3 (*n* = 55)	SCA5 (*n* = 2)	SCA6 (*n* = 22)	SCA7 (*n* = 11)	SCA8 (*n* = 9)	SCA17 (*n* = 5)	
Gender (male), *n* (%)	65 (48.5)	7 (41.2)	7 (53.9)	25 (45.5)	2 (100)	12 (54.6)	4 (36.4)	5 (55.6)	3 (60.0)	0.75
Age of onset, yr. (SD)	41.6 (13.0)	45.3 (10.1)	28.4 (12.3)	41.6 (10.1)	36 (11.3)	54.0 (8.5)	33.9 (14.3)	39.6 (17.1)	33.2 (10.7)	< 0.0001
Age at first ataxia unit visit, yr. (SD)	51.1 (14.0)	53.7 (12.2)	38.5 (13.6)	51.2 (11.9)	59.5 (19.1)	62.4 (8.3)	42.3 (14.6)	52.7 (18.1)	39.2 (10.0)	< 0.0001
Disease duration, yr. (SD)	9.3 (7.2)	8.4 (6.9)	10.1 (10.1)	9.1 (5.9)	23.5 (30.4)	8.4 (4.5)	8.4 (4.2)	13.1 (9.6)	6.0 (2.7)	< 0.0001
BARS score at first visit (SD)	10.1 (5.6)	10.7 (5.4)	9.0 (5.4)	9.6 (5.2)	9.8 (2.5)	10.2 (6.3)	11.2 (6.7)	11.2 (6.4)	11.1 (7.8)	0.08
SCA disease stage, mean (SD)	1.4 (0.7)	1.4 (0.7)	1.3 (0.9)	1.4 (0.7)	1 (0)	1.3 (0.6)	1.4 (0.9)	1.1 (0.9)	1.6 (1.1)	0.47
Stage 0, *n* (%)	9 (6.7)	0 (0)	2 (15.4)	2 (3.6)	0 (0%)	1 (4.6)	1 (9.1)	2 (22.2)	1 (20.0)	
Stage 1, *n* (%)	81 (60.5)	13 (76.5)	6 (46.2)	34 (61.8)	2 (100)	13 (59.1)	7 (63.6)	5 (55.6)	1 (20.0)	
Stage 2, *n* (%)	31 (23.1)	2 (11.8)	4 (30.8)	13 (23.6)	0 (0%)	8 (36.4)	1 (9.1)	1 (11.1)	2 (40.0)	
Stage 3, *n* (%)	13 (9.7)	2 (11.8)	1 (7.7)	6 (10.9)	0 (0%)	0 (0)	2 (18.2)	1 (11.1)	1 (20.0)	
Functional Staging of Ataxia (SD)	2.6 (1.1)	2.7 (1.2)	2.4 (1.1)	2.7 (1.1)	2.7 (1.1)	2.5 (0.7)	2.6 (1.4)	2.4 (1.2)	3.0 (1.6)	0.58
CAG repeat length (where available), median (IQR)		44 (4)	40(5)	72 (6)		22 (0)	43.5 (4.5)	150 (41)	47.5 (8)	

Descriptive statistics on non-missing data. Missing data: disease duration missing in one SCA3 patient. *P* values of chi-square tests for categorical variables and ANOVA for continuous variables

and saccades particularly in SCA7 and SCA2, where 72% (8/11) and 54% (7/13) respectively had non-saccadic pursuits. The presence of nystagmus was also different across the SCAs ($p = 0.0003$), absent in all SCA7 patients, rare in SCA2 (23.1%) and variably present across the other SCAs. Similarly, whereas saccadic hypometria/hypermetria was common in SCA1, 3, and 6, it was infrequent in SCA7 (27.3%) and SCA2 (15.4%; $p = 0.02$). Slowing of saccades was common in SCA 7 and 2, although not invariably present at the first visit (81.8% and 61.5% respectively; $p < 0.0001$), present in 35.3% of SCA3 patients, and rare in other SCAs. Eye movements in primary position and square wave jerks were noted in SCA2, 3, and 7, and ophthalmoparesis was noted in late-stage SCA7, 3, 2, and 1, but these differences were not significant, perhaps due to the small sample size.

The distribution and prevalence of oculomotor abnormalities by disease stage are presented in Fig. 1. In stage 0 ($n = 9$), one of the two SCA2 patients had early saccadic slowing whereas patients with the other SCAs had mainly saccadic pursuit. Stage 1 patients ($n = 81$) had frequent saccadic intrusions (71.6%), nystagmus (59.3%), hypo/hypermetric saccades (59.3%), saccadic slowing (19.8%; mainly SCA7 and

Table 2 Eye movement abnormalities across different SCAs. Abbreviation: SWJ: square wave jerks.

Eye movement abnormality	SCA diagnosis									*p* value
	Total (*n* = 134)	SCA1 (*n* = 17)	SCA2 (*n* = 13)	SCA3 (*n* = 55)	SCA5 (*n* = 2)	SCA6 (*n* = 22)	SCA7 (*n* = 11)	SCA8 (*n* = 9)	SCA17 (*n* = 5)	
Eye movements at rest (SWJ etc), *n* (%)	16 (11.9)	0 (0)	2(15.4)	8 (14.6)	0 (0)	4 (18.2)	0 (0)	1 (11.1)	1 (20.0)	0.575
Saccadic pursuits, *n* (%)	100 (74.6)	12 (70.6)	6 (46.2)	50 (90.9)	1 (50.0)	17 (77.3)	3 (27.3)	7 (77.8)	4 (80.0)	0.0003
Nystagmus (horizontal or vertical), *n* (%)	81 (60.5)	8 (47.1)	3 (23.1)	43 (78.2)	1 (50.0)	19 (88.4)	0 (0)	5 (55.6)	2 (40.0)	< 0.0001
Saccadic hypo/hypermetria, *n* (%)	79 (59.0)	11 (64.7)	2 (15.4)	40 (72.7)	2 (100)	11 (50.0)	3 (27.3)	7 (77.8)	3 (60.0)	0.002
Slowing of saccades, *n* (%)	29 (21.6)	6 (35.3)	8 (61.5)	5 (9.1)	0 (0)	1 (4.6)	9 (81.8)	0 (0)	0 (0)	< 0.0001
Ophthalmoparesis, *n* (%)	7 (5.2)	1 (5.9)	1 (7.7)	3 (5.5)	0 (0)	0 (0)	2 (18.2)	0 (0)	0 (0)	0.539

P values of chi-square tests displayed

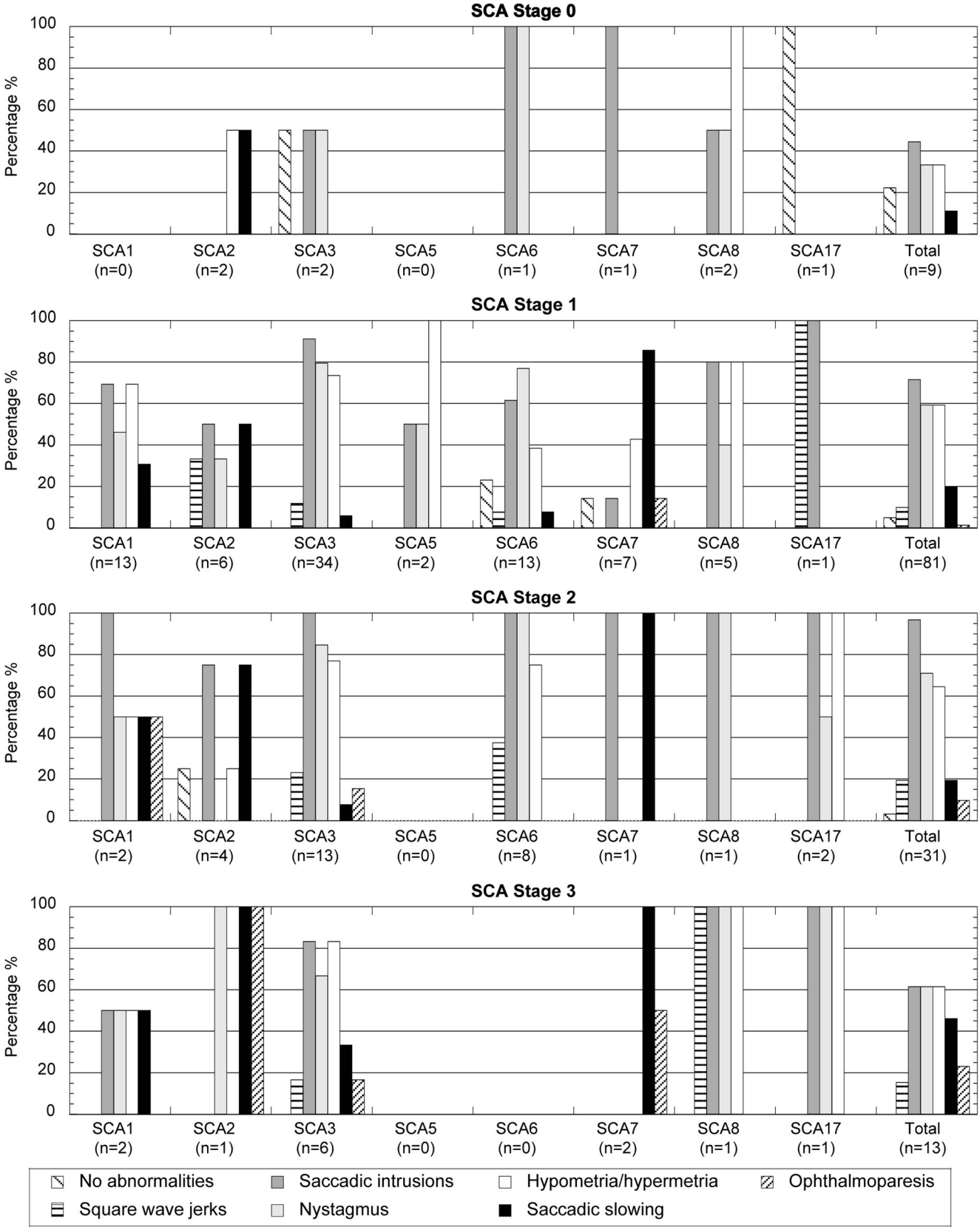

Fig. 1 Distribution and prevalence of oculomotor abnormalities by disease stage. The cluster bar charts describe the prevalence in % of each eye movement abnormality by SCA subtype and within the whole population at each disease stage

SCA2), and rare square wave jerks in primary position (9.9%). Complete external ophthalmoplegia was present only in stage 2 and 3, particularly in SCA2 and SCA7, and less so in SCA1.

For the entire SCA cohort, the burden of oculomotor abnormalities (BARS oculomotor score) correlated with disease stage ($r = 0.485$), FSA ($r = 0.504$), disease duration ($r = 0.294$), disease severity (BARS total minus oculomotor score) ($r = 0.514$), and BARS gait score ($r = 0.493$), all $p < 0.001$ (see Fig. 2). These strong correlations held even in patients within 3 years of disease onset ($n = 25$, all $p < 0.05$). Eye movements were frequently abnormal even in the presence of a normal gait and without appendicular dysmetria. Using linear regression modeling, when controlling for age at first visit, the robust associations with BARS oculomotor score remained highly significant, all $p < 0.003$. For the individual SCAs, correlations were strongest for all measures in SCA1

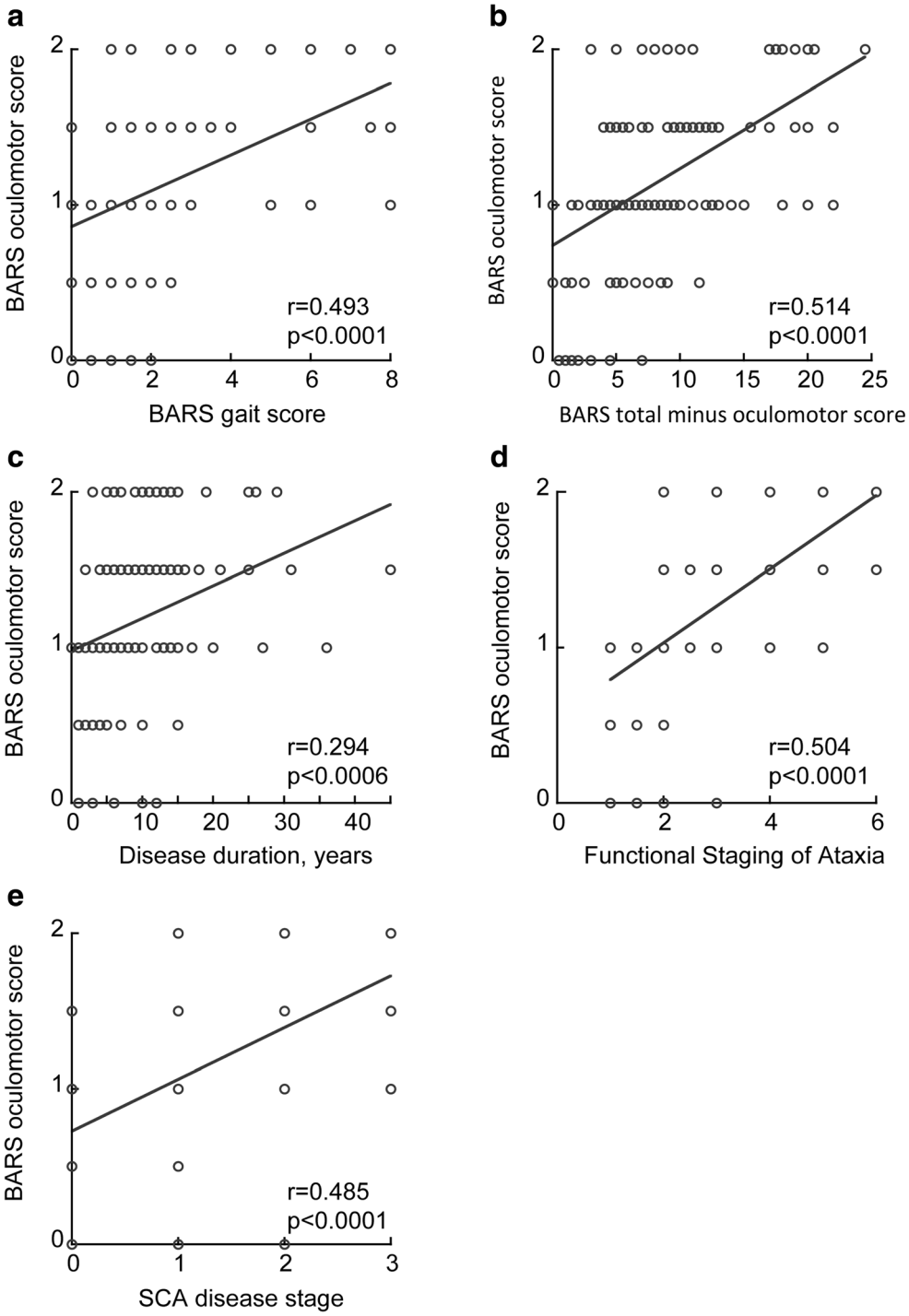

Fig. 2 Univariate regression plots comparing oculomotor abnormalities as assessed by BARS oculomotor score to disease parameters and stage: **a** BARS oculomotor vs BARS gait score; **b** BARS oculomotor vs BARS total score minus oculomotor score; **c** BARS oculomotor score vs disease duration; **d** BARS oculomotor score vs functional staging of ataxia; and **e** BARS oculomotor score vs SCA stage (per Klockgether) [8]. BARS oculomotor score denotes 0.5 point for each of 4 cardinal oculomotor abnormalities (total score 2). Correlation r is the Pearson correlation coefficient and the respective p value

followed by SCA3; however, these did not reach significance in the other SCAs, given small sample sizes or early abnormal oculomotor findings, particularly in SCA7, which presented with early, significant oculomotor slowing (see supplemental Table e-1).

Discussion

We assessed oculomotor findings in a large, mainly early-stage cohort of SCAs at first visit. We observed that oculomotor abnormalities were almost universal, even at first presentation. The burden of oculomotor abnormalities generally correlated with disease stage, duration, and severity; however, in some cases, there was poor correlation likely owing to the early presence of eye movement abnormalities across the SCAs.

Oculomotor abnormalities may represent the only clinical features on examination in early-stage disease [2]. This makes it essential to include eye movement assessment in the neurological examination and in ataxia rating scales, to allow monitoring their nature and evolution over time. The widely-used Scale for the Assessment and Rating of Ataxia (SARA) [10] does not document oculomotor abnormalities, although these were featured in prior scales including the International Cooperative Ataxia Rating Scale and its modified version [5], the newer and shorter BARS [7], and included in the Inventory of Non-Ataxia Signs [11].

Our study conforms to the classical descriptions of cerebellar ataxia, with oculomotor impairments resulting from damage to the oculomotor cerebellum in lobules IX and X (flocculus, paraflocculus, nodulus in the vermis) and vermal lobule VII [12]. It highlights the sensitivity of the oculomotor system to mild, early derangements in cerebellar motor function, and emphasizes the importance of oculomotor evaluation when grading severity of the cerebellar motor syndrome.

These findings have potentially wider implications for the assessment and management of SCA patients, as natural history studies have not yet resolved the critical question of the timing of clinical onset in these diseases [13]. The BARS score documents the presence, but not the severity of oculomotor abnormalities, which is a limitation. Hence, quantitative, observer-independent analysis with non-invasive videooculography may detect oculomotor abnormalities as the earliest manifestations of disease in the SCAs, as has been demonstrated in SCA2 [6] and may provide an objective clinical biomarker of disease onset, as well as severity and progression over time, particularly when disease progression is slow.

Conclusions

The early and ubiquitous presence of objective eye movement abnormalities in the SCAs underscores the need to monitor these findings clinically and with ataxia rating scales. These findings also make the case for the inclusion of quantitative oculography in natural history studies and for potential use in clinical trials of therapeutic and neuroprotective agents in the SCAs.

Author's Contribution Dr. Stephen completed the statistical analysis.

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Compliance with Ethical Standards

This study was approved by the Partners Institutional Review Board Human Studies Committee.

Conflict of Interest The authors declare that they have no conflict of interest. There are no financial relationships deemed relevant to this manuscript for either author. Dr. Schmahmann receives consulting fees from Cadent pharmaceuticals and grant support from the National Ataxia Foundation and the Ataxia Telangiectasia Children's Project. Dr. Schmahmann received financial support from Biohaven and Dr. Stephen received financial support from Biohaven, Sanofi/Genzyme, Bristol-Myers Squibb and Biogen for the conduct of clinical trials.

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