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Longitudinal Changes of Clinical, Imaging, and Fluid Biomarkers in Preataxic and Early Ataxic Spinocerebellar Ataxia Type 2 and 7 Carriers

Giulia Coarelli, MD, PhD, Charlotte Dubec-Fleury, MS, Emilien Petit, MS, Sabrina Sayah, MS, Clara Fischer, MS, Marco Nassisi, MD, PhD, Peggy Gatignol, PhD, Karim Dorgham, PhD, Lina Daghsen, MS, Pierre Daye, PhD, Paulina Cunha, MD, Radhia Kacher, PhD, Rania Hilab, MS, Hortense Hurmic, MS, Antonin Lamazière, PhD, Jean-Charles Lamy, PhD, Marie-Laure Welter, MD, PhD, Marie Chupin, PhD, Jean-François Mangin, PhD, Roger Lane, MD, PhD, Bertrand Gaymard, MD, PhD, Pierre Pouget, PhD, Isabelle Audo, MD, PhD, Alexis Brice, MD, Sophie Tezenas du Montcel, MD, and Alexandra Durr, MD, PhD

Correspondence
Dr. Durr
alexandra.durr@icm-institute.org

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Abstract

Background and Objectives

Brain MRI abnormalities and increases in neurofilament light chain (NfL) have mostly been observed in cross-sectional studies before ataxia onset in polyglutamine spinocerebellar ataxias. Our study aimed to identify longitudinal changes in biological, clinical, and/or imaging biomarkers in spinocerebellar ataxia (SCA) 2 and SCA7 carriers over 1 year.

Methods

We studied SCA2 and SCA7 carriers and controls (expansion-negative relatives) at the Paris Brain Institute. Inclusion criteria included Scale for the Assessment and Rating of Ataxia (SARA) scores between 0 and 15. Assessments at baseline, 6 months, and 12 months comprised neurologic, quality of life, orofacial motor, neuropsychological, and ophthalmologic examinations, along with gait and oculomotor recordings, brain MRI, CSF, and blood sampling. The primary outcome was the longitudinal change in these assessments over 1 year.

Results

We included 15 SCA2 carriers, 15 SCA7 carriers, and 10 controls between May 2020 and April 2021. At baseline, the ages were similar (41 [37, 46] for SCA2, 38 [28.5, 39.8] for SCA7, and 39.5 [31, 54.5] for controls, $p = 0.78$), as well the sex ($p = 0.61$); SARA scores were low but different (4 [1.25, 6.5] in SCA2, 2 [0, 11.5] in SCA7, and 0 in controls, $p < 0.01$). Pons and medulla volumes were smaller in SCAs ($p < 0.05$) and cerebellum volume only in SCA2 ($p = 0.01$). Plasma NfL levels were higher in SCA participants (SCA2: 14.2 pg/mL [11.52, 15.89], SCA7: 15.53 [13.27, 23.23]) than in controls (4.88 [3.56, 6.17], $p < 0.001$). After 1-year follow-up, in SCA2, there was significant pons (-144 ± 60 mm^3) and cerebellum ($-1{,}508 \pm 580$ mm^3) volume loss and a worsening of gait assessment; in SCA7, SARA score significantly increased ($+1.3 \pm 0.4$) and outer retinal nuclear layer thickness decreased (-15.4 ± 1.6 μm); for both SCA groups, the orofacial motor assessment significantly worsened. For preataxic and early ataxic carriers, the strongest longitudinal deterioration on outcome measures was orofacial motility in SCA2 and retinal thickness in SCA7.

From the Sorbonne Université (G.C., C.D.-F., E.P., S.S., L.D., P.C., R.K., R.H., H.H., J.-C.L., M.-L.W., P.P., A.B., S.T.d.M., A.D.), Paris Brain Institute, Inserm, CNRS, INRIA, APHP; CATI (C.F., M.C., J.-F.M.), US52-UAR2031, CEA, Paris Brain Institute, Sorbonne Université, CNRS, INSERM, APHP; Sorbonne Université (M.N., I.A.), Inserm, CNRS, Institut de la Vision; Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts (M.N., I.A.), National Rare Disease Center REFERET and INSERM-DGOS CIC 1423; Sorbonne Université (P.G.), Inserm, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique; Sorbonne Université (K.D.), Inserm, Centre d'Immunologie et des Maladies Infectieuses-Paris (CIMI-Paris), France; P3lab (P.D.), Louvain-la-Neuve, Belgique; Clinical Metabolomic Department (A.L.), Assistance Publique-Hôpitaux de Paris, Saint Antoine Hospital, Saint-Antoine Research Center, Sorbonne University, France; Ionis Pharmaceuticals (R.L.), Carlsbad, CA; and Service de Neurophysiologie (B.G.), University Hospital Pitié-Salpêtrière, Paris, France.

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Glossary

24S-OHC = 24(S)-hydroxycholesterol; **Aβ40** = amyloid beta 40; **Aβ42** = amyloid beta 42; **ASO** = antisense oligonucleotide; **CCAS** = cerebellar cognitive affective syndrome; **CCFS** = Composite Cerebellar Functional Score; **FARS-ADL** = Friedreich Ataxia Rating Scale-Activities of Daily Living; **FACES battery** = dynamic emotional recognition; **HD** = Huntington disease; **INAS** = inventory of nonataxia signs; **MBLF** = Oral-Lingual-Facial Motility; **MBS** = Most Bothersome Symptom; **NfL** = neurofilament light chain; **ONL** = outer nuclear layer; **PCA** = principal component analysis; **polyQ** = polyglutamine; **SARA** = Scale for the Assessment and Rating of Ataxia; **SCA** = spinocerebellar ataxia.

Discussion

Despite the limitation of the small sample size, we detected annual changes in preataxic and early ataxic SCA individuals across brain MRI imaging, clinical scores, gait parameters, and retinal thickness. These parameters could serve as potential end points for future therapeutic trials in the preataxic phase.

Trial Registration Information

ClinicalTrials.gov NCT04288128.

Introduction

Spinocerebellar ataxias (SCAs) caused by coding CAG repeat expansions (SCA1/*ATXN1* [MIM 164400], SCA2/*ATXN2* [MIM 183090], SCA3/*ATXN3* [MIM 109150], SCA6/*CACNA1A* [MIM 183086], SCA7/*ATXN7* [MIM 164500], SCA17/*TBP* [MIM 607136], and DRPLA/*ATN1* [MIM 125370]) are autosomal dominant disorders characterized by a long preataxic phase of several decades.[1] Despite great advances in characterizing the clinical manifestations and genetic underpinnings of the polyglutamine (polyQ) SCAs,[2] much still needs to be done to identify effective therapeutic strategies. Encouraging results for RNA-targeting therapies for polyQ SCAs have been reported in several mouse models.[3-6] Among the most advanced of these approaches is the administration of antisense oligonucleotides (ASOs), which aims to degrade the mRNA encoding the pathologic polyQ protein. A clinical trial with ASO intrathecal injections is ongoing for SCA1 and SCA3 patients (NCT05822908) to assess safety and tolerability primarily. Drug administration at the very earliest symptomatic disease stage or even at a preataxic stage may prevent or delay the emergence of full clinical manifestations of the disease.[7,8]

To date, imaging biomarkers have demonstrated stronger effect sizes than clinical scores in detecting longitudinal changes in SCAs.[9] Previous studies reported cerebellar and brainstem atrophy at the preataxic stages,[10-14] as well as microstructural damage of the white matter[14-17] and magnetic resonance spectroscopy abnormalities[14,18] in the early disease phase. This suggests that halting the natural progression of biomarker changes could be used as outcome proxies in clinical trials, especially for preataxic carriers for whom clinical scales are not discriminant. In this perspective, this longitudinal study aimed at identifying and characterizing biological, clinical, and/or imaging markers in participants with SCA2 and SCA7, either preataxic or at a very early symptom stage, through a multimodal assessment over 1 year of follow-up. The objectives of this study were (1) to determine, in SCA2 and SCA7 carriers compared with healthy controls, the cross-sectional and longitudinal variability for the different parameters/assessments: neurologic examination, quality of life, gait assessment, orofacial motor assessment, neuropsychological assessment, ophthalmologic assessment, oculomotor recording, brain MRI, CSF, and blood biomarkers; (2) to estimate the age at onset and correlate it with the different assessments; and (3) to evaluate changes of measurements over 1 year.

Methods

Study Design and Participants

The "Integrated functional evaluation of the cerebellum" (CERMOI) study was a single-center natural history study for *ATXN2* and *ATXN7* CAG repeat expansion carriers. Eligible criteria were (1) age at least 18 years, (2) genetically confirmed diagnosis of SCA2 (CAG repeat lengths ≥32 in *ATNX2*) or SCA7 (CAG repeat lengths ≥37 in *ATNX7*), (3) Scale for the Assessment and Rating of Ataxia (SARA)[19] score between 0 and 15/40, (4) able to walk independently for a 30-foot distance without an assistive device, and (5) able to undergo cerebral MRI scanning. Eligible healthy controls had to test negative for SCA2 and SCA7 and have a SARA score <3, as well as no other neurologic disease. All participants had to be able to give their informed consent.

The study included 3 visits over a year: at baseline (V1), at month 6 (V2), and month 12 (V3), based on the following assessments: Clinical and neurologic examination including the SARA and the Composite Cerebellar Functional Severity (CCFS)[20] scores, the Inventory of NonAtaxia Signs (INAS),[21] the Most Bothersome Symptom (MBS) questionnaire, and quality of life questionnaires (eMethods section); gait assessment: the instrumented assessments of gait and posture were

performed using an array of 6 body-worn inertial measurement units[22] (eMethods section); orofacial motor assessment: we used the Oral-Lingual-Facial Motility (MBLF) evaluation[23] (eTable 1); neuropsychological evaluation: a comprehensive test battery detailed in eMethods; ocular motor recording and ophthalmologic assessment including functional and imaging analyses[24] (eMethods section); and brain MRI: 3 Tesla cerebral MRI system (Siemens Magnetom PrismaFit) to assess volumetry of brainstem, cerebellum, subcortical volume regions, and cortical thickness (eMethods section). For some participants, MRI data from earlier studies were accessible and were merged to create a more extended longitudinal follow-up. Biosample collections: We measured neurofilament light chain (NfL) and 24(S)-hydroxycholesterol (24S-OHC) levels in plasma and α-synuclein, total tau, pTau181, amyloid beta 40 (Aβ40), and amyloid beta 42 (Aβ42) levels in both plasma and CSF. We measured in blood an expansion index for the CAG repeats in *ATXN2* and *ATXN7* (eMethods section). The schedule of assessments is reported in eTable 2.

Standard Protocol Approvals, Registrations, and Patient Consents

The trial was carried out according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the French Ethics Committee, and all participants provided written informed consent. This trial is registered at ClinicalTrials.gov NCT04288128.

Statistical Analysis

Frequency, percentage, and 95% CIs were used to describe qualitative variables. Quantitative variables were described by their mean and SD or their median and the first and third quartiles (Q1, Q3). Qualitative variables were compared among groups using the Fisher exact test. Quantitative variables were compared among the 3 groups at baseline using the nonparametric Kruskal-Wallis test, followed by the Wilcoxon-Mann-Whitney pairwise test with Hochberg adjustment, when the Kruskal-Wallis p value was significant.

We calculated the estimated age at onset and the estimated disease duration for each genotype. For SCA2, we used a formula previously published[25]; for SCA7, we created a new formula (eMethods section, eFigure 1). Spearman correlations of the outcome variables with the estimated time to onset and the SARA were computed. Using a hypothesis-driven approach, we investigated correlations of the estimated age at onset with pons volume, cerebellum volume, ONL thickness, NfL levels, MBLF score, saccade velocity, lateral step deviation, and instability index at baseline.

We used Mixed Models for Repeated Measures for the longitudinal assessments, using the package *lcmm*.[26] Only random intercept for each participant was used, and the model was fitted with a restricted estimation of maximum likelihood. The overall p value of time across all 3 visits was assessed using a Wald test. For variables with a significant progression, the p values of the differences between V1 vs V2 and V1 vs V3 were estimated with the Satterthwaite method. Effect sizes were calculated as the standardized response mean between V1 and V3. For the pooled data with previous cohorts, we performed linear-mixed models using age as the time variable on the cerebellum and pons volume. A random intercept and a slope were used in the model, and the random slopes were extracted to give each individual a regularized atrophy progression. The linearity of the progression was assessed by verifying the independence of residuals and fitted values. For these longitudinal results, we report the mean annual progression as the mean ± SE of the fixed effect. When reporting value at visits, we give mean ± SD at this visit.

For gait parameters, we performed a principal component analysis (PCA) to describe the relations between all 13 gait parameters. We only analyzed the components that explained more than 10% of the total variance. Individual values in each selected dimension were compared between SCA2, SCA7, and controls with a Kruskal-Wallis test followed by the Wilcoxon-Mann-Whitney pairwise test with Hochberg adjustment.

To account for multiple comparisons, p values were considered significant based on a Holm-adjusted threshold within each set of assessments. Statistical analyses were done with R software (version 4.1.2).

Data Availability

Individual anonymized participant data and relevant clinical study documents will be available for qualified scientific and medical researchers as necessary for doing legitimate research. To request access to the data and submit a research proposal, please send a request to alexandra.durr@icm-institute.org.

Results

Between May 28, 2020, and April 24, 2021, we enrolled 15 SCA2 carriers, 15 SCA7 expansion carriers, and 10 controls at the Paris Brain Institute (ICM).

Baseline Results

Clinical Assessment and Quality of Life

Clinical characteristics and comparisons among groups are shown in Table 1. Symptoms at onset were walking difficulties (n = 8) and dysarthria (n = 2) for patients with SCA2, resulting in a median age at onset of 37 years (Q1 29.5, Q3 44.7). For patients with SCA7, the symptoms at onset were walking difficulties (n = 6) and visual impairment (n = 3) for a median age at onset of 36 years (Q1 17, Q3 48). Five SCA2 and 9 SCA7 carriers were at the preataxia stage (SARA score <3 out of 40). Three preataxic carriers of SCA7 expansions reported age at onset for walking difficulties. At baseline, clinical scores (SARA, CCFS, and INAS) were higher than controls ($p < 0.01$), with no difference between SCA groups (Table 1). Upper motoneuron signs were more frequent in SCA carriers (53% SCA2, 73% SCA7, 0% controls, $p < 0.001$), particularly hyperreflexia in the SCA7 group (73% vs 0%, $p <$

Table 1 Clinical and Genetic Characteristics and Comparison of Preataxic or Early Stage SCA2 and SCA7 Expansion Carriers and Age-Matched Controls at Baseline

	SCA2 (n = 15)	SCA7 (n = 15)	Control (n = 10)	*p* Value[a]	*p* Value[b] SCA2-SCA7	*p* Value[b] SCA2-controls	*p* Value[b] SCA7-controls
Sex							
Women, n (%)	5 (33%)	8 (53%)	4 (40%)	0.61			
Men, n (%)	10 (67%)	7 (47%)	6 (60%)				
Years of education							
Median (Q1, Q3)	15 (14, 17)	16 (14.5, 17)	17 (15.5, 17)	0.43			
Min–max	10–20	11–17	12–20				
CAG repeat length of expanded allele[c]							
Median (Q1, Q3)	38 (36.5, 39)	41 (39, 46.5)		na			
Min–max	35–40	38–62					
Age at baseline, y							
Median (Q1, Q3)	41 (37, 46)	38 (28.5, 39.8)	39.5 (31, 54.5)	0.78			
Min–max	21–66	18–60	26–64				
Age at first symptom, y							
n	n = 8	n = 9					
Median (Q1, Q3)	37 (29.5, 44.7)	36 (17, 48)		0.7			
Min–max	26–60	6–60					
Disease duration, y							
n	n = 8	n = 9					
Median (Q1, Q3)	8.5 (4.2, 11.7)	8 (5, 11)		0.8			
Min–max	1–17	0–12					
SARA score (max value 40)							
Median (Q1, Q3)	4 (1.25, 6.5)	2 (0, 11.5)	0 (0, 0)	0.001	0.93	<0.001	<0.01
CCFS (normal 0.85 ± 0.05)							
Median (Q1, Q3)	0.89 (0.87, 0.95)	0.85 (0.84, 1.03)	0.82 (0.8, 0.84)	0.002	0.45	0.001	0.02
INAS count (max value 16)							
Median (Q1, Q3)	4 (2.5, 4.5)	5 (2.5, 5)	1 (1, 2)	<0.001	0.36	<0.001	<0.001
MBLF (max value 111)							
Median (Q1, Q3)	101 (98.5, 103.5)	103 (98.5, 107.5)	105.5 (101.25, 108)	0.33			
EQ-5D (max value 100)							
Median (Q1, Q3)	80 (62.5, 90)	80 (52.5, 90)	90 (85.5, 98.7)	0.12			
PHQ-9 (max value 27)							
Median (Q1, Q3)	1.5 (0, 2.75)	3 (2, 5)	4.5 (1.5, 6.7)	0.11			
FSS (max value 7)							
Median (Q1, Q3)	1.67 (1.2, 3.4)	2.22 (1.7, 3)	2.56 (2.3, 4.3)	0.22			
FARS-ADL (max value 36)							
Median (Q1, Q3)	3 (0.5, 5)	4 (1, 10)	0 (0, 0)	0.001	0.28	<0.01	<0.01

Continued

Table 1 Clinical and Genetic Characteristics and Comparison of Preataxic or Early Stage SCA2 and SCA7 Expansion Carriers and Age-Matched Controls at Baseline *(continued)*

	SCA2 (n = 15)	SCA7 (n = 15)	Control (n = 10)	*p* Value[a]	*p* Value[b] SCA2-SCA7	*p* Value[b] SCA2-controls	*p* Value[b] SCA7-controls
CCAS (max best 120)							
Median (Q1, Q3)	93 (86, 101.5)	101 (96, 106.5)	105 (102, 108.2)	0.06			

Abbreviations: CCAS = cerebellar cognitive affective syndrome; CCFS = Composite Cerebellar Functional Severity Score; FARS-ADL = Friedreich Ataxia Rating Scale-Activities of Daily Living; FSS = Fatigue Severity Scale; INAS = inventory of nonataxia signs; MBLF = Oral-Lingual-Facial Motility; PHQ-9 = Patient Health Questionnaire-9; SARA = Scale for the Assessment and Rating of Ataxia.
Data are n (%) or median (Q1, Q3). In eTable 3, details of baseline Inventory of nonataxia signs are reported.
[a] *p* Value calculated by Kruskal-Wallis test.
[b] Hochberg adjusted *p* value calculated by Wilcoxon test.
[c] Normal *ATXN2*/SCA2 allele <32 CAG, normal *ATXN7*/SCA7 allele <36 CAG.

0.001, eTable 3). Diametric saccades were more often detected in SCA carriers than controls (73% SCA2, 87% SCA7, 0%, $p < 0.0001$).

The activities of daily living assessed by Friedreich Ataxia Rating Scale-Activities of Daily Living (FARS-ADL) were impaired in SCA groups compared with controls (Table 1).

We collected the Most Bothersome Symptom (MBS) with a dedicated homemade questionnaire. The most reported MBS at baseline was "walking difficulties" (n = 9) for SCA2 and "vision problems" (n = 4) for SCA7 carriers.

Orofacial Motor Assessment

SCA2 carriers had a predominant tremor in the tongue and lips. Co-contractures were notable in the neck, cheeks, eyes, and mouth. We observed hypomimia, slowness, lack of mobility, labial and jugal synkinesia in some patients. The SCA7 carriers showed tremors on the tongue, neck, and eyelids. The "eye" examination part caused palpebral tremors and often revealed a hypomimia with very restricted eyebrow movements. We also observed a slowness in performing lingual movements and articulatory imprecision. The median of the total oral motor mobility score at baseline was similar among groups (Table 1) and for the subscores and nerves scores (eTable 4).

The median SARA subscore for dysarthria showed no differences between SCA carriers and controls ($p = 0.07$). Dysphagia, assessed by INAS item, was mild in 9 patients with SCA with a SARA score ranging from 1.5 to 12.5 and moderate in 2 patients with SCA7 with a SARA score of 15. The median dysphagia score was 0 (Q1 0, Q3 0) in controls, 0 (Q1 0, Q3 0.5) in SCA2, and 0 (Q1 0, Q3 2) in SCA7, with a difference only between SCA7 carriers and controls ($p = 0.045$).

Ophthalmologic Assessment

For SCA7 group, retinal involvement was detected in both functional and imaging examinations already at preataxic stage.[24] For SCA2 group, no alterations were found in any structural and imaging analyses.

Oculomotor Biomarkers

The saccade main sequence, resulting from the relationship between amplitude, duration, and velocity of saccades, was altered in manifest SCA2 (n = 10) and SCA7 (n = 5) expansion carriers vs controls ($p < 0.05$) (eFigure 3). Square wave jerks were present in 8 SCA2 carriers (5 preataxic and 3 ataxic) and 10 SCA7 carriers (9 preataxic and 1 ataxic), with a trend to disappear with disease progression measured by SARA (eFigure 4). We did not find difference in median saccade amplitude and velocity between SCA carriers and controls (eTable 5).

Gait Assessment

We performed a principal component analysis, finding 3 components that explained, respectively, 47%, 13%, and 11% of the total variance of the groups. The first component had stronger loading on the speed, stride length, toe-off angle, and swing; the second component on the variability of the gait cycle and stride length, and the step cadence; and the third component on the pitch initial, the foot strike angle, and the elevation at midswing. Using the first 2 components, we differentiated controls from patients with ataxia (eFigure 5). Patients with SCA7 with SARA score >10 presented greater variability of stride length, gait cycle, and lateral step deviation. Patients with SCA2 and SCA7 with SARA scores between 5 and 10 presented higher speed, cadence, swing, and toe-off angle (eFigure 5). SCA2 and SCA7 carriers presented a different gait impairment: The first component was affected in SCA2 ($p = 0.04$), whereas the second component was different in SCA7 ($p < 0.01$). The details of the 2-minute gait assessment are reported in eTable 6.

Neuropsychological Evaluation

We analyzed data resulting from Cerebellar Cognitive Affective Syndrome (CCAS) scale, executive functions, attentional skills, and social cognition showing no difference compared with controls (eTable 7). The CCAS score was slightly lower for SCAs, but not significantly different ($p = 0.06$, Table 1). At the last visit (V3), we added an assessment for emotional recognition with dynamic stimuli evaluated by the FACES battery. We found a worse performance only for SCA7 compared with SCA2 carriers (31 [Q1 29, Q3 32.5] vs 34 [Q1 31.5, Q3 34], respectively, $p = 0.04$) and controls (31 [Q1 29,

Table 2 Comparison of Baseline Cerebellum and Brainstem Volumes Between SCA Carriers and Controls

Variable	SCA2 (n = 15)	SCA7 (n = 15)	Control (n = 10)	*p* Value[a]	*p* Value[b] SCA2-SCA7	*p* Value[b] SCA2-control	*p* Value[b] SCA7-control	Holm *p* value
Cerebellum	69.9 (64.9, 74.3)	82.8 (76.2, 89.7)	85.7 (83.7, 88.7)	0.0021	0.01	0.004	0.285	0.0038
Right cerebellum	35 (32.3, 36.9)	41.9 (38.1, 44.6)	42.8 (41.6, 44.3)	0.002	0.007	0.007	0.461	0.0042
Gray matter	25.5 (23.4, 28.4)	30.5 (28.2, 32)	31.4 (29.2, 32.1)	0.003	0.008	0.009	0.723	0.0056
White matter	9.98 (8.39, 10.9)	10.7 (9.82, 13.1)	12.4 (11.4, 13.4)	0.01	0.129	0.009	0.129	0.01
Left cerebellum	34.8 (32.8, 37.4)	41 (37.9, 45.2)	42.9 (42, 44.4)	0.001	0.007	0.004	0.261	0.0038
Gray matter	25.7 (23.8, 28.2)	29.4 (29.1, 32.5)	31.4 (30.1, 32.3)	0.002	0.006	0.006	0.643	0.0045
White matter	9.49 (7.96, 10.8)	10 (9.67, 12.7)	12.1 (11.3, 12.5)	0.008	0.16	0.003	0.16	0.008
Vermis	5.1 (4.55, 5.33)	5.33 (4.9, 6.2)	5.61 (5.28, 5.9)	0.161				0.025
Gray matter	4.05 (3.61, 4.23)	4 (3.86, 4.84)	4.3 (4.08, 4.44)	0.39				0.05
White matter	1.11 (1.02, 1.29)	1.22 (0.995, 1.4)	1.37 (1.21, 1.44)	0.066				0.0125
Midbrain	4 (3.87, 4.28)	3.94 (3.68, 4.31)	4.54 (4.2, 4.66)	0.069				0.0167
Pons	7.2 (6.57, 8.92)	9.09 (7.12, 10.4)	10.9 (10.7, 11.4)	0.004	0.267	0.002	0.03	0.0071
Medulla oblongata	3.08 (2.81, 3.28)	3.26 (2.99, 3.53)	3.6 (3.54, 3.88)	0.003	0.412	0.004	0.007	0.0063
SCP	0.157 (0.142, 0.166)	0.136 (0.125, 0.159)	0.18 (0.176, 0.195)	0.003	0.148	0.023	0.003	0.005
Right cerebellum hemisphere								
Lobule III	0.191 (0.161, 0.308)	0.257 (0.222, 0.294)	0.249 (0.211, 0.305)	0.414				0.0167
Lobule IV	0.975 (0.854, 1.08)	0.978 (0.935, 1.12)	1 (0.944, 1.13)	0.635				0.05
Lobule V	2.04 (1.89, 2.27)	2.43 (1.98, 2.92)	2.17 (2.05, 2.68)	0.122				0.0125
Lobule VI	4.77 (4.2, 5.67)	5.84 (5.27, 6.49)	5.8 (5.3, 6.1)	0.012	0.023	0.023	0.723	0.0026
Lobule crus I	7.87 (6.83, 8.7)	8.86 (8.45, 9.76)	9.25 (8.42, 9.54)	0.020	0.038	0.038	0.935	0.0038
Lobule crus II	4.88 (4.63, 5.84)	6 (5.61, 6.69)	5.9 (5.54, 6.3)	0.005	0.009	0.019	0.849	0.0024
Lobule VIIB	2.85 (2.5, 2.96)	3.04 (2.77, 3.3)	3.51 (2.95, 3.77)	0.028	0.148	0.035	0.311	0.0045
Lobule VIIIA	3.62 (3.06, 3.9)	3.99 (3.54, 4.29)	4.01 (3.87, 4.45)	0.056				0.0063
Lobule VIIIB	2.05 (2, 2.42)	2.57 (2.21, 2.79)	2.65 (2.46, 2.75)	0.02	0.123	0.024	0.285	0.0036
Lobule IX	1.77 (1.56, 2.18)	2.09 (1.95, 2.51)	2.38 (2.19, 2.48)	0.033	0.135	0.049	0.338	0.005
Lobule X	0.382 (0.353, 0.434)	0.437 (0.398, 0.507)	0.509 (0.424, 0.527)	0.016	0.135	0.013	0.311	0.0031
Left cerebellum hemisphere								
Lobule III	0.175 (0.156, 0.255)	0.239 (0.199, 0.281)	0.285 (0.275, 0.3)	0.019	0.091	0.041	0.091	0.0033
Lobule IV	1.07 (0.875, 1.23)	1.11 (0.985, 1.3)	1.18 (1.01, 1.35)	0.464				0.025
Lobule V	2.14 (1.88, 2.36)	2.5 (2.23, 2.94)	2.58 (2.47, 3.02)	0.025	0.045	0.045	0.849	0.0042
Lobule VI	4.88 (4.41, 5.56)	5.74 (5.21, 6.14)	5.98 (5.49, 6.15)	0.013	0.027	0.027	0.643	0.0028
Lobule crus I	7.81 (6.65, 8.44)	8.48 (7.99, 9.58)	8.59 (8.44, 9.04)	0.06				0.0071
Lobule crus II	4.83 (4.18, 5.28)	5.76 (5.23, 6.37)	5.71 (5.38, 6.11)	0.006	0.017	0.013	0.849	0.0025
Lobule VIIB	2.66 (2.31, 2.97)	3.12 (2.88, 3.36)	3.39 (3.23, 3.53)	0.0007	0.011	0.001	0.071	0.0021
Lobule VIIIA	3.67 (3.12, 4.19)	4.04 (3.65, 4.52)	4.27 (3.9, 4.46)	0.085				0.01
Lobule VIIIB	2.5 (2.1, 2.64)	2.69 (2.52, 2.99)	2.72 (2.49, 2.96)	0.074				0.0083
Lobule IX	1.73 (1.57, 2.14)	2.18 (1.93, 2.58)	2.36 (2.11, 2.62)	0.016	0.091	0.024	0.261	0.0029

Continued

Table 2 Comparison of Baseline Cerebellum and Brainstem Volumes Between SCA Carriers and Controls *(continued)*

Variable	SCA2 (n = 15)	SCA7 (n = 15)	Control (n = 10)	*p* Value[a]	*p* Value[b] SCA2-SCA7	*p* Value[b] SCA2-control	*p* Value[b] SCA7-control	Holm *p* value
Lobule X	0.379 (0.35, 0.404)	0.433 (0.376, 0.467)	0.516 (0.435, 0.539)	0.046	0.232	0.068	0.238	0.0056

Abbreviation: SCP = superior cerebellar peduncle.
In this table, we reported volume in ‰ of intracranial volume as median scores (Q1, Q3) of cerebellum and brainstem regions. *p* Values are reported before and after the Holm adjustment.
[a] *p* Value calculated by Kruskal-Wallis test.
[b] Hochberg adjusted *p* value calculated by Wilcoxon test.

Q3 32.5] vs 34 [Q1 34, Q3 34], respectively, $p = 0.02$). For SCA7 carriers, the test was not affected by vision problems because neutral and joyful faces were always recognized. The least recognized expression was sadness (3.8 ± 1.45), followed by anger (4.9 ± 0.88) and disgust (5.2 ± 0.86).

Brain MRI

Pons, medulla oblongata, and superior cerebellar peduncle volumes were significantly decreased in both SCA2 and SCA7 groups compared with controls (Table 2). Cerebellum volume was significantly decreased only in SCA2 (Table 2). Among cerebellum lobules, after Holm adjustment, only the left VIIB lobule volume was smaller in SCA2 carriers compared with controls ($p = 0.001$) and SCA7 carriers ($p = 0.01$, Table 2, eTable 8).

The subcortical regions of interest and the cortical thickness were not different between SCA carriers and controls (eTable 8).

Fluid Biomarkers

The median plasma NfL levels were higher in SCA2 and SCA7 carriers compared with controls ($p < 0.001$, Table 3). Aβ40, Aβ42, total Tau, pTau181, and αSyn were similar among groups in plasma and CSF. Plasma 24S-OHC were lower in SCA2 compared with SCA7 carriers ($p < 0.01$), but not different from controls ($p = 0.12$) with similar cholesterol levels ($p = 0.25$) (Table 3).

We explored the somatic mosaicism of the CAG repeat expansion in *ATXN2* and *ATXN7*: the blood instability index was higher in SCA7 than in SCA2 carriers (1.32 [Q1 0.98, Q3 2.2] vs 0.51 [Q1 0.33, Q3 0.6], $p < 0.0001$) (Table 3).

Estimated Disease Duration and Correlations With the Different Assessments

Bland-Altman plots showed no mean bias because the difference between reported age at onset and estimated age at onset was not different from 0 (SCA2: 2.0 [Q1 −0.8; Q3 5.7] $p = 0.38$, SCA7: −0.4 [Q1 −6.5; Q3 3.7], $p = 0.65$, eFigure 2). As expected, for both SCA2 and SCA7 groups, we found that the SARA score started to increase when the estimated disease duration was close to the time 0 and continued linearly to increase with the estimated disease duration ($\rho = 0.51$, $p = 0.05$ for SCA2 and $\rho = 0.82$, $p = 2e\text{-}04$ for SCA7, eFigure 6). For SCA7 carriers, there was a significant worsening with increased disease duration but not for SCA2 carriers (Figure 1). However, the SARA score correlated with the pons and cerebellar atrophy and with the lateral step deviation and instability index for the SCA2 group and for all parameters except the cerebellum volume for SCA7 group (Figure 2).

Plasma NfL levels started to increase compared with controls more than 10 years before the estimated disease onset for both SCAs, followed by the pons and then cerebellum volume loss (Figure 1).

Longitudinal Results

After 12 months, 2 preataxic SCA7 carriers progressed to the ataxic stage (SARA ≥3). The progression of clinical scores at V2 and V3 showed a significant increase in SCA7 individuals with an annual change of 1.3 ± 0.4 points per year (Table 4, all analyses in eTable 9).

At month 12, "walking difficulties" (n = 6) was confirmed as the main MBS for SCA2 carriers and "sleep disturbance" (n = 3) for SCA7 carriers, eFigure 7. For controls, "fatigue" (n = 3) and "sleep disturbance" (n = 2) were the most reported MBS. Quality of life did not worsen at V2 and V3 (eTable 9).

We found a significant aggravation of gait parameters in SCA2 individuals (eTable 10). The most affected parameter was the lateral step deviation with an annual increase of 0.0024 ± 0.0009, $p = 0.014$ (Table 4). Using PCA, there was a trend of worsening in SCA2 (first component $p = 0.02$, Holm threshold $p = 0.017$; second component $p = 0.046$, Holm threshold $p = 0.025$). For the SCA7 group, no modification at 1-year follow-up was detected (eTable 10).

For both SCAs, the MBLF score worsened at each time point (Table 4), with an annual variation for MBLF score of −11.3 ± 2.4, $p < 0.0001$ for SCA2 carriers and −8.9 ± 1.4, $p < 0.0001$ for SCA7 carriers. At month 12, all MBLF subscores and nerves scores (except for mandibular branch of trigeminal nerve) were significantly decreased in both SCA groups at month 12 (eTable 11). For nerves scores, progression was detected at V2 in both SCA groups for hypoglossal nerve score ($p = 0.01$ for SCA2 and $p < 0.0001$ for SCA7, eTable 11).

Table 3 Comparison of Baseline Fluid Biomarkers Among the 3 Groups

Variable	SCA2 (n = 15)	SCA7 (n = 15)	Control (n = 10)	*p* Value[a]	*p* Value[b] SCA2-SCA7	*p* Value[b] SCA2-control	*p* Value[b] SCA7-control	Holm *p* value
Plasma								
NfL, pg/mL	14.2 (11.5, 15.8)	15.53 (13.2, 23.2)	4.88 (3.5, 6.1)	<0.001	0.17	<0.001	<0.001	0.008
Aβ40, pg/mL	226.6 (197.7, 252.9)	249.9 (209.39, 264)	262.9 (230.2, 269)	0.29				
Aβ42, pg/mL	10.65 (9.2, 11.6)	10.24 (9.2, 12)	12.65 (11.52, 13.6)	0.13				
Tau, pg/mL	5.9 (5.1, 7.2)	6.84 (5.73, 8)	6.48 (5.54, 7.6)	0.61				
pTau181, pg/mL	1.74 (1.5, 1.9)	1.39 (1.24, 3)	1.53 (1.36, 1.9)	0.52				
αSyn, pg/mL	22,700.5 (18,059, 54,444)	28,937 (16,249, 53,844)	35,142.5 (23,809, 68,628)	0.43				
24-OH, ng/mL	21.1 (10.7, 22.6)	27.7 (24.6, 35.8)	25.3 (16.8, 31.8)	0.005	0.0014	0.24	0.45	0.006
Cholesterol, mg/dL	174 (163, 206)	179 (146, 258)	201 (168, 236)	0.25				
CAG instability index	0.51 (0.33, 0.6)	1.32 (0.98, 2.2)		<0.0001	<0.0001	—	—	0.01
CSF	n = 15	n = 14	n = 8					
Aβ40, pg/mL	7,764.7 (3,478.1, 9,672.7)	8,195.7 (6,514, 9,756)	11,229.6 (7,547, 11,567)	0.07				
Aβ42, pg/mL	533.8 (263.5, 806.6)	641.27 (545.8, 703)	898.9 (572, 989.1)	0.16				
Tau, pg/mL	127.9 (65, 162.4)	136.5 (119.1, 191)	115.6 (74.3, 125.4)	0.12				
pTau181, pg/mL	26.67 (19.3, 34.1)	30.84 (26.65, 38)	27.3 (23.4, 29.6)	0.27				
αSyn, pg/mL	866.7 (289.9, 1,719)	1,180.1 (750.8 1,769)	1,141.9 (471, 1,598)	0.37				

Abbreviations: Aβ40 = amyloid beta 40; Aβ42 = amyloid beta 42.
Data are expressed as median (Q1, Q3). *p* Values are reported before and after the Holm adjustment.
[a] *p* Value calculated by Kruskal-Wallis test.
[b] Hochberg adjusted *p* value calculated by Wilcoxon test.

Among all structural and imaging ophthalmologic parameters, ONL thickness showed a significant reduction in the SCA7 group over 1 year (Table 4), with an annual variation of −15.4 ± 1.6 μm ($p < 0.0001$).

For brain MRI, the regions that showed a significant volume loss after 12-month follow-up were the cerebellum and the pons for SCA2 carriers (Table 4). This volume loss represents an annual atrophy rate of −1,508 ± 580 mm^3 for the cerebellum and −144 ± 60 mm^3 for the pons. For SCA7 carriers, the progression was not significant (−697 ± 583 mm^3 and −120 ± 74 mm^3, respectively). For a subgroup of participants, 7 SCA2 and 4 SCA7 carriers, previous longitudinal scans were available that allowed us to follow the pons and cerebellum volume loss for up to 10 years (Figure 3). The annual rate of atrophy was linear over time and significantly different between SCAs for the cerebellum with −1,679 ± 718 mm^3 in SCA2 carriers and −675 ± 112 mm^3 in SCA7 carriers ($p = 0.012$) but similar for the pons with −317 ± 161 in SCA2 mm^3 and −172 ± 51 mm^3 in SCA7 ($p = 0.16$). The other regions for which a trend of progression was shown, for SCA2 and SCA7 pooled together, were the total cerebellar volume, the cerebellar gray matter, the midbrain, cerebellum lobules (VI, Crus I, Crus II, VIIB, IX, X), the putamen, the insula, and medial orbitofrontal cortical thickness (eTables 12 and 13).

NfL levels remained stable after 1-year follow-up for SCA2 and SCA7 groups (15.01 ± 5.14 pg/mL, $p = 0.23$ and 17.81 ± 11.16 pg/mL, $p = 0.14$, respectively). For controls, NfL increased over 1 year (5.16 ± 2.38 pg/mL at baseline vs 7.93 ± 3.68 pg/mL at V3, $p < 0.001$). Among the other biomarkers, the progression was detected only for α-synuclein between baseline and month 6 for the SCA7 group ($p < 0.01$). All other biomarkers were stable over 1 year (eTable 14).

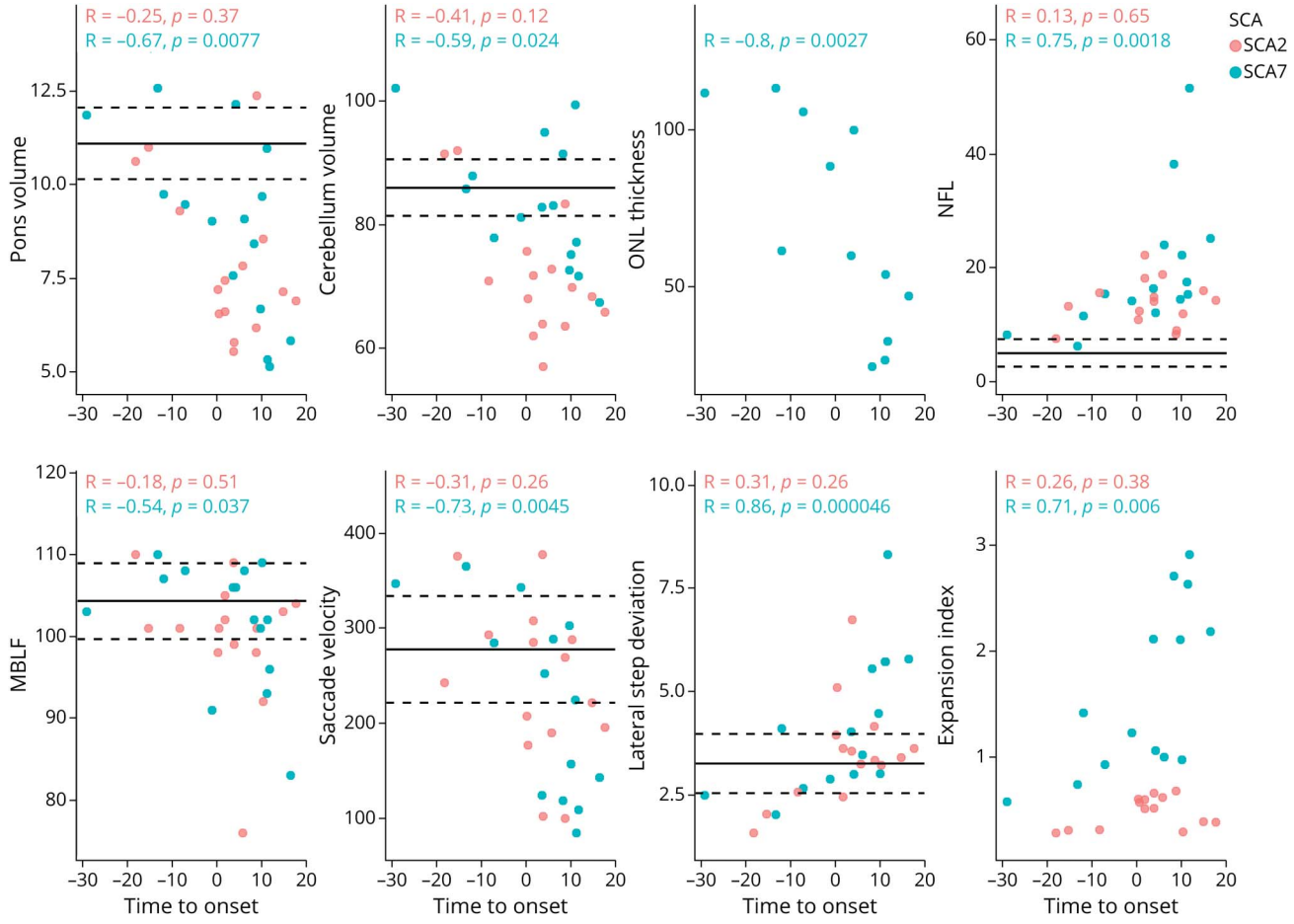
The instability index of CAG expansion increased after 12 months in SCA2 and SCA7 pooled together with a median variation of 0.014 (Q1 0.004, Q3 0.05), $p < 0.001$. Taken separately, this result was confirmed for both SCA groups with a variation of 0.006 (Q1 −0.002, Q3 0.03, $p = 0.03$) for SCA2 and a variation of 0.024 (Q1 0.001, Q3 0.074, $p = 0.008$) for the SCA7 group.

For oculomotor recording and neuropsychological examination, we did not detect any change over 1 year (eTable 15).

Outcomes for Therapeutic Trials in SCA2 and SCA7 Carriers

Based on our longitudinal results from baseline to 12-month follow-up, we estimated the sample size for future therapeutic trials in SCA2 and SCA7 carriers using the parameters that

Figure 1 Correlation Between Time to Onset and the Variables of Interest Different Between SCA and Controls



Plasma NfL levels started to increase compared with controls more than 10 years before the estimated disease onset for both SCAs, followed by the pons and then cerebellum volume loss. The black solid line is the mean value for controls with the 95% CI in the dashed line. Spearman correlations were computed. Saccade velocity related to saccades of 5–10°, and pons and cerebellum volumes are reported in cm^3. EI = expansion index (for CAG repeat); MBLF = Oral-Lingual-Facial Motility; NFL = plasma neurofilament light chain; ONL = outer nuclear layer; SCA = spinocerebellar ataxia.

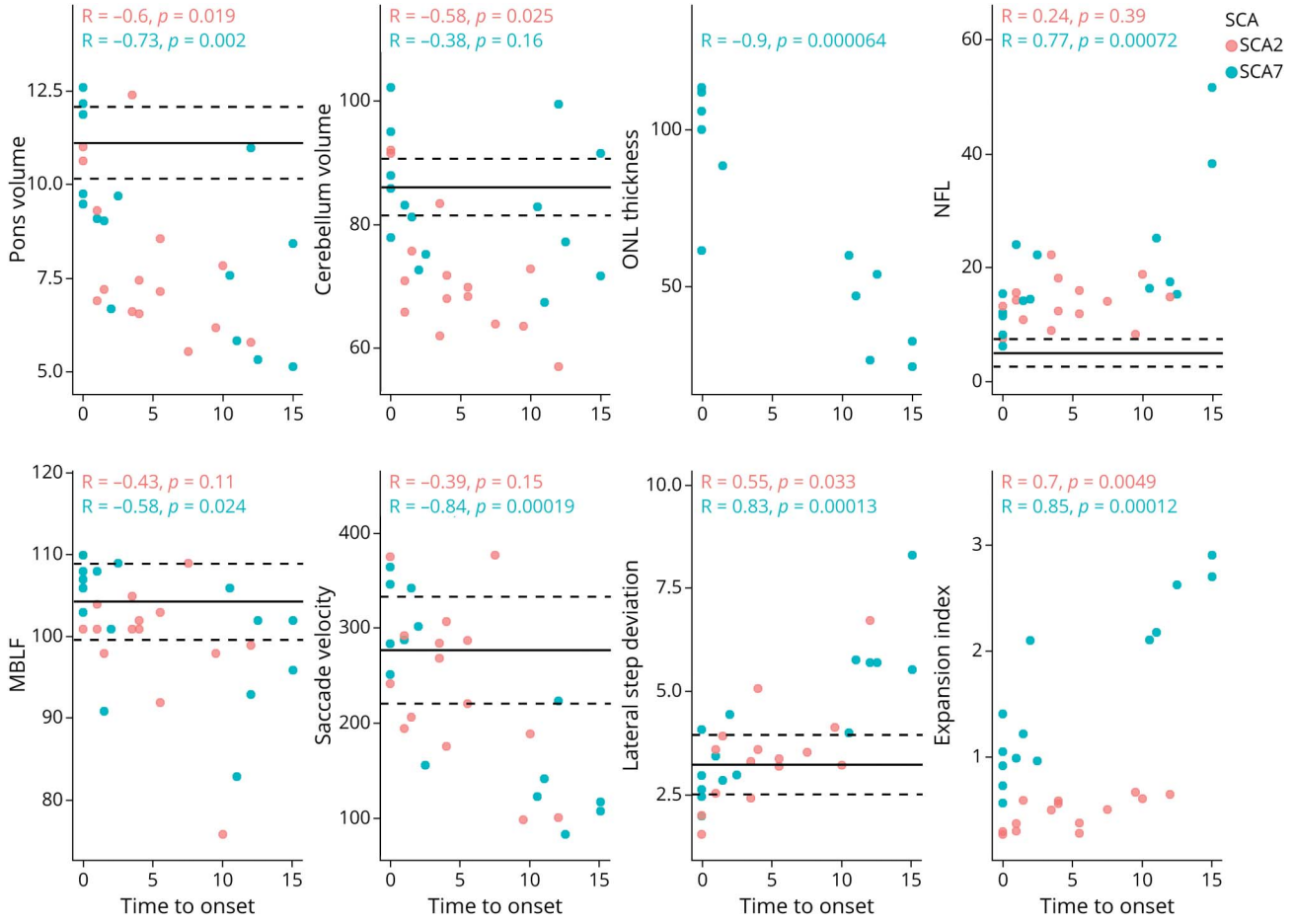
worsened over 12 months as the outcome variable (Table 4). For preataxic and early ataxic carriers, the strongest outcome was the orofacial motor score (MBLF score) in SCA2 and retinal ONL in SCA7. For ophthalmologic clinical trials using as first outcome the ONL thickness, the required total sample size would be 28 individuals for a power of 80% to detect a therapeutic effect size of 50% over 1 year.

Discussion

We report a longitudinal multimodal assessment in the preataxic and early ataxic stages in SCA2 and SCA7. We detected significant changes over 1 year in SARA scores, cerebellar and pons volumes, ONL thickness, orofacial motor scores, and lateral step deviation (Table 4). These measurements could be used as end points in a 1-year trial with a sample size of less than 40 individuals. Despite the inclusion of preataxic individuals, the sample size here reflects that of moderately ataxic SCA2 individuals.[27] This is in line with the assumption that the pathologic process is linear as observed in Huntington disease (HD).[28]

We report for the first time the SARA longitudinal change for SCA7 with an increase of 1.3 ± 0.4 points per year. We confirmed this progression in a larger SCA7 group from our SPATAX cohort (of 1.24 ± 0.26 points per year n = 58, unpublished data). This aligns with SARA progression reported for the other polyQ SCAs.[29] We detected preataxic pyramidal signs in both SCA groups, especially for SCA7 carriers. Pyramidal involvement can hence precede the cerebellar ataxia, as also described for other SCAs.[1] This questions the definition of preataxic as "presymptomatic" and favors the inclusion of these individuals in neuroprotective or preventive trials. In addition, the recent biological classification of HD with an integrated staging system was marked by indicators of underlying pathophysiology.[30] For SCA3, a staging was also proposed based on a cohort of ataxic and preataxic individuals.[31] Our report constitutes the basis for SCA2 and SCA7 staging with a large multimodal approach.

Figure 2 Correlation Between SARA and the Variables of Interest Different Between SCA and Controls



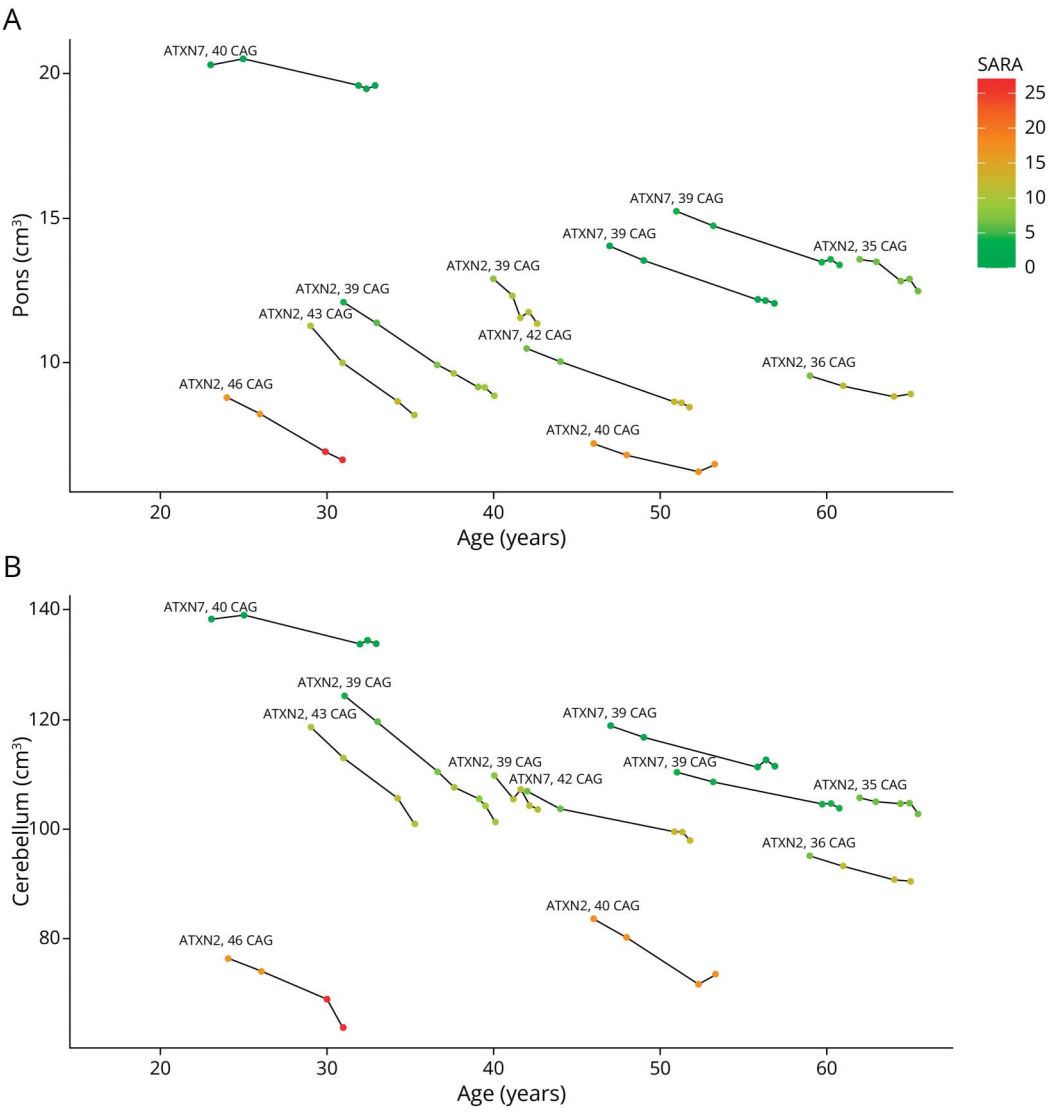
For SCA7, all parameters (except for the cerebellum volume) significantly worsened with SARA score increase. For SCA2, this correlation was significant for pons and cerebellum volumes, lateral step deviation, and expansion index. The black solid line is the mean value for controls with the 95% CI in the dashed line. Spearman correlations were computed. Saccade velocity related to saccades of 5–10°, and pons and cerebellum volumes are reported in cm^3. EI = expansion index (for CAG repeat); MBLF = Oral-Lingual-Facial Motility; NFL = plasma neurofilament light chain; ONL = outer nuclear layer; SCA = spinocerebellar ataxia.

Table 4 Longitudinal Progression Over 1-Year Follow-Up and Relative Effect Size

SCA	Variable	Global *p* value	Baseline, mean (SD)	V2 (M6), mean (SD)	*p* Value baseline-V2	V3 (M12), mean (SD)	*p* Value baseline-V3	SRM	Sample size (1 arm)
SCA2	Pons	0.009	7.93 ± 2.04	7.94 ± 2.06	0.92	7.83 ± 2.09	0.009	0.59	184
	Cerebellum	0.023	71.79 ± 10.20	71.46 ± 10.72	0.41	70.73 ± 10.96	0.007	0.59	181
	MBLF	<0.001	100.0 ± 8.0	91.6 ± 12.3	<0.001	88.7 ± 9.8	<0.001	1.84	20
	Lateral step deviation	0.004	3.51 ± 1.24	3.84 ± 1.10	0.003	3.91 ± 1.23	0.007	0.82	95
SCA7	ONL	<0.001	68.8 ± 33.7	54.4 ± 33.3	<0.001	53.3 ± 34.7	<0.001	2.2	14
	MBLF	<0.001	101.7 ± 7.8	97.3 ± 8.4	0.001	92.7 ± 8.0	<0.001	1.44	32
	SARA	0.002	5.53 ± 6.19	6.53 ± 7.7	0.013	6.9 ± 7.5	<0.001	0.78	105

Abbreviations: MBLF = Oral-Lingual-Facial Motility; ONL = outer nuclear layer; SARA = Scale for the Assessment and Rating of Ataxia; SRM = standardized response mean.
Mixed-effect models were used to assess the significance of the longitudinal progression with random intercepts and fixed visit effects. The global *p* value is the *p* value of the Wald test for the nullity of the visits 2 and 3 effects. SRM was computed between V1 and V3. Sample sizes were computed with the SRM, for a 50% reduction of the variation with 80% power. Therefore, it gives the sample sizes for 1 arm needed to detect a significant difference (with 80% power) of a 50% reduction in progression compared with natural history over 1 year. For pons and cerebellum volume, the data are expressed as a percentage of intracranial volume. All other longitudinal results are reported in eMethods.

Figure 3 Longitudinal Progression of Pons and Cerebellum Atrophy up to 10-Year Follow-Up



In this figure, we report the progression of pons (A) and cerebellum (B) volumes in CERMOI individuals (7 SCA2 and 4 SCA7 carriers) who participated in 2 previous longitudinal studies (BIOSCA, NCT01470729 and ATRIL, NCT03347344). The volume loss is quite linear during the follow-up period. The ataxia severity scored by the SARA scale is illustrated by the color code on the right. For each participant, the gene and the CAG repeat size are reported.

Pons atrophy is a solid biomarker, evident already in SCA2 and SCA3 preataxic carriers[10-12,14,32] and with a huge effect size compared with clinical scores.[9,33] The annual rate of cerebellar atrophy was gene-specific, lower in SCA7 carriers indicating a more brainstem driven disease than in SCA2. The brain MRI follow-up reported here, which covers a 10-year period starting at preataxic stages, allowed us to confirm the linear volume loss over time in both structures. This represents the longest longitudinal study of volume loss in SCA2 and SCA7 compared with previous studies.[9,12,13]

Most of the carriers showed cone dystrophy, already at the preataxic stage. This finding is not age-related, but it is rather correlated with the CAG repeat size and the severity of cerebellar ataxia.[24] ONL thickness correlated with SARA and NfL levels,[24] proving to be a surrogate biomarker, useful for ophthalmologic therapeutic trials.

We report a new assessment, sensitive to longitudinal progression over 1 year in both SCA groups, the orofacial motor assessment.[23] Assessing orofacial motility is important because dysarthria and dysphagia significantly affect the quality of life of patients with SCA. Notably, dysphagia is the main cause of death in SCA1, due to motoneuronal loss in the hypoglossal motor nucleus.[34,35] It manifests in advanced stages, as evidenced in our cohort, with ataxic carriers experiencing moderate dysphagia. At baseline, participants presented mild hypomimia, slowness, tremors, co-contractures, and synkinesia that significantly changed over as already reported in Friedreich ataxia.[23]

Gait analysis indicated that lateral step deviation was the most sensitive parameter to changes in SCA2 carriers. These data confirm a previous report on a larger SCA2 cohort.[22] High variability of spatiotemporal gait parameters, wide-base support, reduced cycle duration, and stride length are characteristic of ataxic locomotion and discriminative of SCA carriers compared with controls.[36]

We showed a very early increase in NfL levels more than 10 years before the estimated age at onset, followed by the pons and then cerebellum volume loss. This result confirms NfL as a valid disease activity biomarker for SCAs because its levels are already high at the preataxic stage and increase with the disease course, correlating with clinical scores.[1,37-39] Preataxic individuals with pyramidal signs showed NfL levels close to the pathologic cutoff reported in our previous SCA cohort.[40] NfL levels can more accurately predict the age at onset of cerebellar symptoms compared with other parameters,[38] such as imaging biomarkers, because NfL can detect neurodegeneration before changes become apparent in volumetric MRI.[31] Therefore, NfL levels could allow to stratify preataxic carriers by their likely proximity to onset, which could be useful for designing clinical trials. Even if its level does not change longitudinally, NfL may be prognostic for the rate of disease progression overall in the preataxic phase. In addition, NfL levels can be used to monitor treatment safety. In HD, a dose-dependent increase in NfL levels was observed in patients treated with tominersen compared with those receiving a placebo in the phase 3 study.[41] Moreover, NfL level could decrease in response to effective disease-modifying treatment as shown in the tofersen study for SOD1 amyotrophic lateral sclerosis.[42] The somatic instability in the blood of the CAG repeat expansion, expressed as expansion index, increased over 1 year in both SCA groups. This instability starts to increase several years before the estimated age at onset, with a higher expansion index for the SCA7 group (Figure 1). This could be another biomarker for carriers' stratification, and it should be more investigated because DNA repair genes and somatic instability modify the disease onset and progression in HD and polyQ SCAs.[43] The other plasma and CSF biomarkers (24-OHC, α-synuclein, total Tau, pTau 181, Aβ40, Aβ42) did not change longitudinally. For 24S-OHC, we found a lower level in SCA2, as has already been reported,[44] but not in SCA7 carriers. Further validation of these fluid biomarkers leveraging larger cohorts will be crucial to conclude their reliability.

Patient-reported outcome measures are particularly relevant for monitoring treatment effects. At baseline, activities of daily living assessed by FARS-ADL were impaired in both patients with SCA2 and SCA7. The other questionnaires exploring health status, depression, and fatigue reported similar scores among the 3 groups. Because health-related quality of life and functional assessments are not sensitive enough for preataxic stages and longitudinally, we used a questionnaire to investigate the most bothersome symptom. The walking problems were confirmed to be the most annoying after 1-year follow-up for patients with SCA2, whereas for patients with SCA7, vision and sleep problems were the most reported. However, complaints changed over visits, reflecting fluctuations in health status in the early stages.

We explored a large battery of tests for cognitive assessment. The CCAS scale[45] was not sensitive enough to identify subtle cognitive impairment at an early stage. Interestingly, emotional recognition assessed by the FACES battery showed poorer performance in SCA7 carriers. The recognition of facial emotions, an important component of social cognition, is affected in patients with Friedreich ataxia[46] and patients with SCA, possibly relating to a defect in the corticocerebellar network.[47-49] Semantic fluency was impaired in both SCA groups, but not different after correcting for multiple comparisons.

One of the limitations of our study is the small sample size. This was primarily due to the rarity of SCA2 and SCA7. In addition, setting the inclusion criterion at a SARA score below 15 further narrowed the pool of potential participants. Given the exploratory nature of the multimodal approach, adjusting for multiple comparisons reduced the significance threshold for each variable. The inclusion of preataxic and early ataxic patients, who will be the target of future disease-modifying therapies is a strength of the study. The overall usefulness of these data lies in the effect size calculations for significant outcomes that showed longitudinal changes, demonstrating that the sample sizes do not exceed those required for the ataxic stages. ONL thickness stands out as the strongest end point for a clinical trial in SCA7, rendering a study targeting the retina very feasible. In SCA2, clinical end points appear more powerful than imaging end points, as evidenced by the smaller required sample sizes. Our findings reveal significant changes over 1 year in both clinical and imaging biomarkers for SCA2 and SCA7 carriers, identified even before the ataxia onset. This insight allows us to foresee therapeutic strategies for preataxic individuals,[8] leveraging the utility of these end points that are reasonably likely to predict clinical outcomes.

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Appendix Authors

Name	Location	Contribution
Giulia Coarelli, MD, PhD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Charlotte Dubec-Fleury, MS	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Analysis or interpretation of data
Emilien Petit, MS	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Sabrina Sayah, MS	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Major role in the acquisition of data
Clara Fischer, MS	CATI, US52-UAR2031, CEA, Paris Brain Institute, Sorbonne Université, CNRS, INSERM, APHP, Ile de France, France	Analysis or interpretation of data
Marco Nassisi, MD, PhD	Sorbonne Université, Inserm, CNRS, Institut de la Vision; Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, National Rare Disease Center REFERET and INSERM-DGOS CIC 1423, Paris, France	Major role in the acquisition of data
Peggy Gatignol, PhD	Sorbonne Université, Inserm, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France	Major role in the acquisition of data
Karim Dorgham, PhD	Sorbonne Université, Inserm, Centre d'Immunologie et des Maladies Infectieuses-Paris (CIMI-Paris), Paris, France	Major role in the acquisition of data
Lina Daghsen, MS	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Major role in the acquisition of data
Pierre Daye, PhD	P3lab, Louvain-la-Neuve, Belgique	Analysis or interpretation of data
Paulina Cunha, MD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Major role in the acquisition of data
Radhia Kacher, PhD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Major role in the acquisition of data
Rania Hilab, MS	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Major role in the acquisition of data
Hortense Hurmic, MS	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Major role in the acquisition of data
Antonin Lamazière, PhD	Clinical Metabolomic Department, Assistance Publique-Hôpitaux de Paris, Saint Antoine Hospital, Saint-Antoine Research Center, Sorbonne University, France	Major role in the acquisition of data
Jean-Charles Lamy, PhD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Major role in the acquisition of data
Marie-Laure Welter, MD, PhD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Analysis or interpretation of data
Marie Chupin, PhD	CATI, US52-UAR2031, CEA, Paris Brain Institute, Sorbonne Université, CNRS, INSERM, APHP, Ile de France, France	Analysis or interpretation of data
Jean-François Mangin, PhD	CATI, US52-UAR2031, CEA, Paris Brain Institute, Sorbonne Université, CNRS, INSERM, APHP, Ile de France, France	Analysis or interpretation of data
Roger Lane, MD, PhD	Ionis Pharmaceuticals, Carlsbad, CA	Drafting/revision of the manuscript for content, including medical writing for content
Bertrand Gaymard, MD, PhD	Service de Neurophysiologie, University Hospital Pitié-Salpêtrière, Paris, France	Study concept or design
Pierre Pouget, PhD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Analysis or interpretation of data
Isabelle Audo, MD, PhD	Sorbonne Université, Inserm, CNRS, Institut de la Vision; Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, National Rare Disease Center REFERET and INSERM-DGOS CIC 1423, Paris, France	Major role in the acquisition of data; analysis or interpretation of data
Alexis Brice, MD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Drafting/revision of the manuscript for content, including medical writing for content
Sophie Tezenas du Montcel, MD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Analysis or interpretation of data
Alexandra Durr, MD, PhD	Sorbonne Université, Paris Brain Institute, Inserm, CNRS, INRIA, APHP, France	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

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