Progression of biological markers in spinocerebellar ataxia type 3: longitudinal analysis of prospective data from the ESMI cohort

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Summary

Background Spinocerebellar ataxia type 3 (SCA3) is an autosomal dominantly inherited adult-onset disease. We aimed to describe longitudinal changes in clinical and biological findings and to identify predictors for clinical progression.

Methods We used data from participants enrolled in the ESMI cohort collected between Nov 09, 2016 and July 18, 2023. The data freeze included data from 14 sites in five European countries and the United States. We assessed ataxia with the Scale for the Assessment and Rating of Ataxia (SARA). We measured disease-specific mutant ataxin-3 protein (ATXN3) and neurofilament light chain (NfL) in plasma and performed MRIs. Data were analysed by regression modelling on a timescale defined by onset. The onset of abnormality of a marker was defined as the time at which its value, as determined by modelling, exceeded the mean ± 2 SD of healthy controls. To study responsiveness of markers, we determined the sensitivity to change ratios (SCSs).

Findings Data from 291 SCA3 mutation carriers before and after clinical onset and 121 healthy controls were included. NfL levels became abnormal in SCA3 mutation carriers more than 20 years (−21.5 years [95% CI n.d.–9.5]) before onset. The earliest MRI abnormality was volume loss of medulla oblongata (−4.7 years [95% CI n.d.–3.3]). The responsiveness of markers depended on the disease stage. Across all stages, pons volume had the highest responsiveness with an SCS of 1.35 [95% CI 1.11–1.78] exceeding that of SARA (0.99 [95% CI 0.88–1.11]). In SCA3, lower age ($p = 0.0459$ [95% CI of slope change −0.0018 to 0.0000]) and lower medulla oblongata volume ($p < 0.0001$ [95% CI of slope change −0.0298 to −0.0115]) were predictors of SARA progression.

Interpretation Our study provides quantitative information on the progression of biological markers in SCA3 mutation carriers before and after onset of ataxia, and allowed the identification of predictors for clinical progression. Our data could prove useful for the design of future clinical trials.

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Keywords: Spinocerebellar ataxia; MRI; NfL; ATXN3; Disease modelling; Staging model; Biomarker

Research in context

Evidence before this study

We searched Medline and ISI Web of Science for reports published before Nov 30, 2024, with the search terms [“spinocerebellar ataxia type 3” AND “biomarker” OR “ATXN3” OR “neurofilament light chain (NfL)” OR “MRI” AND “prospective” OR “follow-up” OR “longitudinal”]. Only peer-reviewed, English-language reports of human cohort studies with at least 10 participants were considered. In a previous analysis of 33 SCA3 mutation carriers from this cohort, plasma concentrations of mutant ATXN3 remained stable over one year. In a two-year follow-up study of 19 SCA3 patients, NfL concentration did not change. Six studies with participant numbers ranging from 17 to 23 and follow-up times from six months to five years found progressive atrophy of a number of brain structures and cervical spinal cord, as well as increasing abnormalities of diffusion parameters of a number of brain fibre tracts.

Added value of this study

In this European, longitudinal registry study (ESMI), we prospectively investigated a large cohort of SCA3 mutation carriers before and after onset. We determined the sequence and extent of plasma mutant ATXN3 and NfL, as well as MRI measure changes along the disease course. This study is, to the best of our knowledge, the first to comprehensively study multimodal biological markers longitudinally over the entire disease course of SCA3. Our data allowed to determine the onset of abnormality of the studied biological markers, define their stage-specific sensitivity to change, and identify predictors for clinical progression.

Implications of all the available evidence

The available data provide quantitative information on the progression of biological markers in SCA3 mutation carriers before and after the onset of ataxia, and allow the identification of predictors of clinical progression. Knowledge of the progression of biological markers in these individuals can help researchers to design trials of interventions aimed at slowing clinical progression or delaying the onset of ataxia.

Introduction

Spinocerebellar ataxia type 3 (SCA3) is the most common autosomal dominantly inherited adult-onset ataxia disease worldwide. SCA3 takes a progressive course and leads to increasing disability and premature death. It is caused by unstable expansions of polyglutamine encoding CAG repeats within the *ATXN3* gene, resulting in the formation of abnormally elongated, misfolded ataxin-3 protein (ATXN3).[1]

Targeted therapies for SCA3 are being developed, and first safety trials of antisense oligonucleotides (ASOs) have been initiated (https://clinicaltrials.gov, NCT05160558, NCT05822908). In the future, preventive intervention in mutation carriers before clinical onset will be a realistic option.[2] With the advent of disease-modifying treatments for SCA3, there is the need to identify biological markers that are sensitive to disease-related change before and after clinical manifestation. Mutant ATXN3 can be measured at low concentrations in the CSF and plasma of mutation carriers, but is absent in healthy controls.[3,4] Blood neurofilament light chain (NfL) is an easily accessible, non-specific marker of neurodegeneration.[5] In cross-sectional studies, NfL was increased in patients and in mutation carriers before onset.[6–10] In a two-year follow-up study of 19 SCA3 patients, the increased NfL concentrations did not change.[9] In longitudinal MRI studies of SCA3 mutation carriers, progressive atrophy of the cerebellum, pons, mesencephalon, and cervical spinal cord was observed.[11–14] In addition, diffusion parameters of cerebellar peduncles, superior longitudinal fasciculus, corona radiata, and medial lemniscus showed increasing abnormalities.[13–15]

The European Spinocerebellar ataxia type 3/Machado-Joseph disease Initiative (ESMI) initiated a longitudinal registry study of SCA3 mutation carriers before and after clinical onset representing a wide spectrum of disease severity. Analysis of cross-sectional clinical, as well as fluid biomarker and MRI volumetric data allowed to draft a data-driven model of disease stages for SCA3.[16] In the present study, we describe longitudinal changes of mutant ATXN3, NfL and several MRI measures that were abnormal in SCA3 mutation carriers before onset. We focused the analysis on determining stage-specific sensitivity of biological markers and identifying predictors of clinical progression.

Methods

Study design and participants

The study population of the ESMI registry study consists of (1) SCA3 mutation carriers before and after onset, (2) persons at risk to carry the SCA3 mutation (first degree relatives of SCA3 patients) who have not been diagnostically tested, and who do not wish to be tested, and (3) healthy controls (including spouses, unrelated persons, and persons at risk who were negatively tested). The genetic status of persons at risk (first degree relatives of SCA3) was assessed within a central scientific genetic testing. Results of these central scientific genetic tests were used to assign persons at risk either to the

SCA3 mutation carrier or healthy control group, but not disclosed to the study participants.

The ESMI registry study is conducted at 14 sites in five European countries and the United States. Participants undergo annual standardized assessments including clinical examination and biosample collection. MRI is performed at 11 sites.

Procedures

We used the Scale for the Assessment and Rating of Ataxia (SARA)[17] to assess the presence and severity of ataxia. Manifest ataxia was defined by a score of ≥ 3.[17,18]

Analysis of the CAG repeat length of the *ATXN3* gene was performed at the Department of Medical Genetics of the University of Tübingen (Tübingen, Germany). Determinations were done for 243 mutation carriers and 20 persons at risk who had not been diagnostically tested. For 42 SCA3 mutation carriers, from whom no DNA was available, information about CAG repeat lengths was taken from medical records; in eight participants, no information on repeat length was available.

Plasma concentrations of mutant ATXN3 were measured using an ultrasensitive immunoassay based on the SMC® technology.[3] Plasma concentrations of NfL were determined with the Neurology 4-Plex A assay (N4PA) (Quanterix, Billerica, MA, United States) run on the Simoa HD-X Analyzer™.[7] Samples were analysed using two different assay lots. For each sample, measurements were performed in split duplicates, and the average values were calculated.

T1-and diffusion weighted MRIs were acquired on Siemens 3T scanners (Siemens Medical Systems, Erlangen, Germany). As imaging biological markers, we calculated 61 brain volumes including brainstem and cerebellar sub-segments and the mean diffusion metrics (fractional anisotropy (FA), medial diffusivity (MD), axial (AD) and radial diffusivity (RD)) of 14 white matter tracts. Details of the MR sequences and imaging analysis as well as a comprehensive list of all studied volumes and white matter tracts are given in the Appendix pp 4–5.

Definition of axes and disease stages

Age of onset was defined as the reported first occurrence of gait disturbances.[19] The onset of reported gait disturbances is different from the time of conversion to manifest ataxia, defined by a SARA cut-off of ≥3.The time of onset defined as the time of the first occurrence of gait abnormalities reported by a mutation carrier has been used, because (i) it refers to a reference time point that can be determined retrospectively, while the observed conversion of SARA to values ≥3 is only available in a minority of cases, (ii) it represents a core symptom of ataxia which appears in all patients, and is a milestone with relevance to the patient, (iii) mathematical models, related to the reported onset of gait disturbances are available and allow to estimate the time to onset in mutation carriers, not yet experiencing gait disturbances (negative values).[20] In contrast, SARA is an examiner-based assessment of ataxia severity. As mentioned above, there are currently not enough data sets available with observed changes from values < 3 to values ≥ 3, that would allow to establish estimation models. 36 SCA3 mutation carriers had not yet experienced gait disturbances (right-censored individuals). In nine SCA3 mutation carriers with gait disturbance, information on the reported age of onset was missing (left-censored individuals). In these 45 SCA3 mutation carriers, the age of onset was estimated, as described below.

For regression, NfL concentrations and MRI measures were z-transformed with respect to age and sex. Z-scores of MRI volumes and FA values were inverted, so that higher z-scores indicate increasing abnormality in all measures. Since SARA scores and mutant ATXN3 in healthy controls were close to 0, no z-transformation was performed, and the raw values were used. A Box-Cox transformation with parameter $\lambda = 0.25$ was applied to the SARA score to approximate normality. Following recently proposed definitions of SCA3 disease stages,[16] SCA3 mutation carriers were assigned to the carrier stage (SARA <3 and NfL z-score <2), biomarker stage (SARA <3 and NfL z-score ≥2), or ataxia stage (SARA ≥3).

Statistical analysis

General statistical approach

Statistical analysis was carried out using R version 4.3.1 (R Core Team 2023: R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria).

The selection of MRI parameters was based on the group comparison between pre-ataxic SCA3 mutation carriers with a SARA <3 and healthy controls using linear regression models. Details on the statistical methods and test results are given in the Appendix pp 6–7.

Five NfL values, one ATXN3 value, and one pons volume value were excluded as outliers after visual inspection of the data (Appendix p 2).

To relate fluid and MRI biomarker data to the time from onset, we applied a conditional multiple imputation approach.[16] First, censored values of age of onset were imputed fitting a previously published parametric survival model.[20] For this, the last follow-up visit of each participant was considered and the time from onset for towards each visit date was then calculated respectively. To account for censoring, age of onset was imputed with the conditional expectation for right-censored individuals (accounting for actual age) and with the unconditional expectation for left-censored individuals. Second, SARA score and biological markers were regressed on the (imputed) time from onset using additive mixed regression models with participant-specific random intercepts and a cubic P-spline with six B-spline basis functions and a second-order difference penalty. This two-step procedure was repeatedly applied to 1000 bootstrap samples from the original sample. Final estimates of the spline coefficients and associated variance estimates were then calculated by applying Rubin's rule.

Onset of abnormality in fluid and MRI markers

A biological marker was considered abnormal, if its value, as determined by modelling, exceeded the normal range defined by mean ± 2 SD in healthy controls. Onset of abnormality was defined as not determinable (n.d.) if the intersection between the normal range and the fitted spline function of the upper and lower limit of the 95% CI, respectively, was not reached within the time interval of observations (33 years before to 41 years after onset).

Sensitivity to change of clinical, fluid and MRI measures

Responsiveness of SARA and biological markers was assessed by calculating sensitivity to change ratios (SCSs).[21] To this end, linear mixed regression models with the (imputed) time from onset as the time variable and participant-specific random intercepts were fitted for the entire disease course and each stage (carrier, biomarker, ataxia), respectively. SCSs were then calculated by dividing the estimated slopes of progression by the estimated standard deviation of the slopes. 95% CIs of the SCSs were determined by non-parametric bootstrap based on 1000 samples. Higher SCS values indicate greater sensitivity to change of the respective measure.

Predictors of clinical *progression*

For prediction of SARA increase, we applied univariable and multivariable mixed regression models with the Box-Cox transformed SARA as outcome and age, sex, CAG repeat length of the expanded allele and the baseline values of the biological markers as covariates. We tested the effect of these factors on SARA progression by interactions with the time variable (time from onset). The multivariable model was selected by stepwise selection with the Bayesian information criterion including all covariates with $p < 0.05$ in univariable models (or $p < 0.15$, see Appendix p 11). We conducted the univariable analysis for the entire disease course and each stage (carrier, biomarker, ataxia), respectively, while we restricted the multivariable model to the entire disease course to ensure a sufficiently large sample size.

Ethic approval

The study was approved by the ethics committees of all contributing centres. Approval numbers and dates for the leading national site: London, UK: Research Ethics Committee (REC) name: London–Chelsea Research Ethics Committee; REC Reference number: 17/LO/0381; Approval date: 28/04/2017; Bonn, Germany: Ethics committee, Medical Faculty, University of Bonn, 176/16; date of approval: 11th Oct 2016, Amendment1 17th Sep 2020, Amendment2: 27th Aug 2024; Nijmegen, The Netherlands: CMO (Regio Arnhem-Nijmegen); European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease (ESMI); 2016–2554 (local), NL25267.091.16 (national); Approval date: April 3rd, 2017; Santander, Spain: COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS DE CANTABRIA; 2018.282, Date of approval: 01/02/2019 and 26/04/2021 (Amendment 1); Coimbra, Portugal: Ethics committee of the Faculty of Medicine of the University of Coimbra. Date of approval: CE-085/2017 (date 25.09.2017), amendment CE-121/2020 (date 20.01.2020); Minnesota, USA: Ethics committee Univ. of Minnesota, IRB study number 0502M67488, date of approval: June 9, 2017). At enrolment, informed and written consent following the Declaration of Helsinki was obtained from all study participants. The study protocol is available online (https://ataxia-esmi.eu/study-protocols).

Role of the funding source

The study funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Enrolment and cohort characteristics

Between Nov 09, 2016, and Jul 18, 2023, we enrolled 419 participants with at least one available biological marker. Seven participants and biomarker data from 39 visits were excluded. A flow chart detailing the reasons is given in the Appendix p 2. Eventually, 291 SCA3 mutation carriers and 121 healthy controls were included in the analysis. Among the SCA3 mutation carriers, 55 had no ataxia (SARA <3), and 236 had ataxia (SARA ≥3) at baseline. At baseline, mutant ATXN3 concentrations were available in 97, NfL concentrations in 303, and MRI results in 171 participants. Baseline characteristics of the study participants and the subgroups with available biological markers are given in Table 1.

Data from 856 visits were analysed. Participants had a median number of 2 (IQR 1–3) visits and a median observation time of 1.02 years (0.00–2.03). Hundred-and-two SCA3 mutation carriers and 33 healthy controls completed one follow-up visit, 64 mutation carriers and 14 healthy controls two follow-up visits, and 31 mutation carriers and 13 healthy controls three to five follow-up visits. The Appendix details the availability of ATXN3, NfL and MRI data at the follow-up visits (Appendix p 3).

	Healthy controls	SCA3 mutation carriers with SARA < 3	SCA3 mutation carriers with SARA ≥ 3
Total group (n = 412)			
Number of participants	121 (29%)	55 (13%)	236 (57%)
Women	71 (59%)	30 (55%)	113 (48%)
Age, years	44.6 (34.3–56.3)	34.6 (29.1–39.9)	52.2 (45.2–60.3)
SARA score	0.0 (0.0–0.5)	1.0 (0.5–2.0)	12.0 (8.5–19.0)
Length of expanded CAG allele	n.a.	68 (65–71)	69 (66–71)
Time from onset, years	n.a.	−12.5 (−16.8 to −0.0)	10.1 (5.6–14.9)
ATXN3 subgroup (n = 97)			
Number of participants	10 (10%)	14 (14%)	73 (76%)
Women	6 (60%)	8 (57%)	29 (40%)
Age, years	49.1 (31.8–57.5)	34.2 (29.4–37.6)	51.6 (44.9–60.2)
SARA score	0.0 (0.0–0.0)	1.0 (0.3–1.5)	10.5 (7.5–16.5)
Length of expanded CAG allele	n.a.	69 (65–71)	69 (64–71)
Time from onset, years	n.a.	−14.6 (−18.1 to −10.7)	8.3 (4.9–13.2)
NfL subgroup (n = 303)			
Number of participants	92 (30%)	32 (10%)	179 (59%)
Women	55 (60%)	18 (56%)	90 (50%)
Age, years	44.8 (35.7–56.6)	34.2 (26.2–39.7)	51.9 (45.3–59.7)
SARA score	0.0 (0.0–0.7)	1.0 (0.5–1.6)	13.0 (8.5–20.6)
Length of expanded CAG allele	n.a.	69 (66–71)	69 (66–72)
Time from onset, years	n.a.	−12.6 (−16.7 to −2.7)	10.9 (6.4–15.9)
MRI subgroup (n = 171)			
Number of participants	45 (26%)	32 (19%)	94 (55%)
Women	25 (56%)	21 (66%)	38 (40%)
Age, years	45.8 (32.7–56.3)	34.2 (29.5–40.8)	51.8 (45.3–58.2)
SARA score	0.0 (0.0–0.5)	1.0 (0.4–2.0)	10.0 (8.0–14.5)
Length of expanded CAG allele	n.a.	68. (65–71)	69 (67–71)
Time from onset, years	n.a.	−12.3 (−17.6 to 2.0)	8.7 (4.6–12.6)

Data are n, n (%), or median (IQR). NfL = neurofilament light chain. SARA = Scale for the Assessment and Rating of Ataxia.

Table 1: **Baseline characteristics of study participants.**

Baseline results of ATXN3 concentrations, NfL concentrations, and MRI measures are given in Appendix p 8. Mutation carriers without ataxia had higher ATXN3 and NfL concentrations, lower medulla oblongata, pons, midbrain, cerebellar white matter (CWM), and superior cerebellar peduncle (SCP) volumes, reduced FA inferior cerebellar peduncle (ICP) and FA SCP, and increased RD ICP values than healthy controls. Because our focus was on early disease stages, we took into account only those MRI measures, which were altered in mutation carriers without ataxia in comparison to healthy controls (Appendix p 7). In addition, we included cerebellar grey matter (CGM) volume, to be consistent with the previously published cross-sectional analysis of this cohort.[16]

At baseline, nine of the SCA3 mutation carriers were in the carrier stage, 23 in the biomarker stage, and 236 in the ataxia stage. Twenty-three mutation carriers without ataxia could not be assigned to a disease stage, because NfL concentrations were not available. Within the observation period, two mutation carriers converted from the carrier to the biomarker stage, and seven from the biomarker to the ataxia stage. On the other hand, one mutation carrier assigned to the biomarker stage at baseline was assigned to the carrier stage at the final visit. Further, three mutation carriers, which were scored as ataxic at baseline, were assigned to earlier stages at the final visit: two to the biomarker and one to the carrier stage.

Onset of abnormality of fluid and MRI markers

Progression of SARA scores, mutant ATXN3, NfL concentrations, and MRI measures of SCA3 mutation carriers in relation to the time from onset are shown as modelled curves in Fig. 1. The original data displayed as spaghetti plots are given in the Appendix p 9.

SARA progression had a sigmoidal shape (Fig. 1A). Scores crossed the cut-off of 3, which defines the onset of the ataxia stage, 4.2 years [95% CI n.d.–0.9] before the reported or estimated onset of gait disturbances (Table 2). At the time of onset of gait disturbances, the SARA score was 4.7 [2.5–7.9]. Mutant ATXN3 concentrations were constant throughout the entire disease course without major changes over time so that the onset of abnormality could not be determined (Fig. 1B). NfL concentrations increased throughout the disease course, but the increase slowed down after onset (Fig. 1C). NfL values became abnormal more than 20 years (−21.5 years [n.d. to −9.5]) before onset (Table 2). All analysed MRI volumes and diffusion measures worsened over time, albeit at different rates and with different slopes (Fig. 1D–F). Medulla oblongata volume (−4.7 years [n.d. to +3.7]), FA ICP (−2.1 years [−10.3 to 2.7]), and pons volume (−0.6 years [−6.4 to 3.8]) became abnormal before onset. The remaining MRI measures became abnormal 0.3–14.4 years after onset in the following temporal order: RD ICP, CWM volume, midbrain volume, SCP volume, and FA SCP. CGM value did not decrease more than 2 SD below the mean of healthy controls throughout the entire disease course (Table 2). Compared to our previous cross-sectional analysis, in which we determined the upper 95% CI limits of NfL, pons volume, and CWM volume, the onset of abnormality of these measures was 3.8–6.5 years later. To clarify the reason for this difference, we calculated the upper 95% CI limits of NfL, pons volume, and CWM volume based alone on the baseline values of the present dataset. These values differed only by 1.1–3.2 years from the previously determined values (Appendix p 12).

Sensitivity to change of clinical, fluid and MRI measures

To determine the responsiveness of the studied measures, we calculated the SCSs. For the entire disease, all measures except ATXN3 had SCSs larger than 0. The most sensitive measure was pons volume with an SCS of 1.35 [95% CI 1.11–1.78]. Further stage-specific analyses showed that the SCSs of the various outcome measures depended on the disease stage. In the carrier

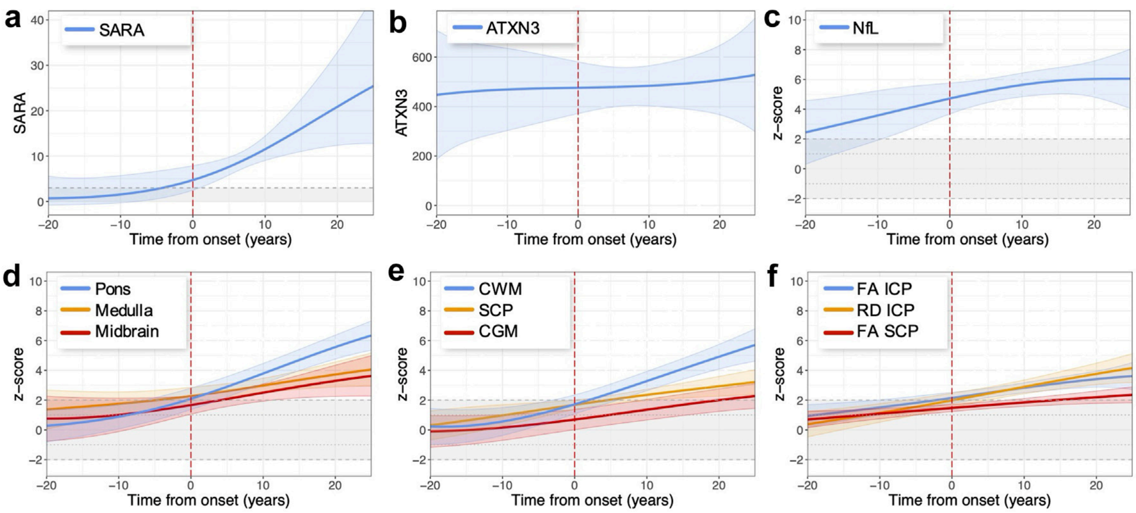

Fig. 1: Progression of (a) SARA, (b) ATXN3, (c) NfL, (d) MRI brainstem volumes, (e) MRI cerebellar volumes, and (f) MRI diffusion measures in SCA3. Data were analysed by additive mixed regression models with participant-specific random intercepts on a timescale defined by onset of gait disturbances (vertical dashed line in red) using a cubic P-spline with six B-spline basis functions. The estimated 95% CIs are shown by the shaded areas around the curves. NfL and MRI data were z-transformed in relation to healthy controls. Z-scores of MRI volumes and FA values were inverted for a better visualisation. The horizontal ribbon shaded in grey indicates the normal range (±2) of the z-transformed measures (NfL, MRI measures) of healthy controls. For SARA the applied cut-off of 3 is indicated by a dotted horizontal line. CGM = cerebellar grey matter. CWM = cerebellar white matter. FA ICP = fractional anisotropy of the inferior cerebellar peduncle. FA SCP = fractional anisotropy of the superior cerebellar peduncle. NfL = neurofilament light chain. RD ICP = radial diffusivity of the inferior cerebellar peduncle. SCP = superior cerebellar peduncle.

Outcome	Onset of abnormality in years	95% CI
Clinical		
SARA	−4.2	n.d.–0.9
Fluid		
Mutant ATXN3	n.d.	n.d.–n.d.
NfL	−21.5	n.d. to −9.5
MRI volume		
Medulla oblongata	−4.7	−n.d. to 3.7
Pons	−0.6	−6.4 to 3.8
Midbrain	4.1	n.d.–11.4
CWM	2.0	−3.0 to 5.9
CGM	n.d.	9.4–n.d.
SCP	4.6	0.1–10.8
MRI diffusion measures		
FA ICP	−2.1	−10.3 to 2.7
RD ICP	0.3	−6.4 to 5.0
FA SCP	14.4	7.7–n.d.

The onset of abnormality of a marker was defined as the time at which its value, as determined by modelling, exceeded the mean ± 2 SD of healthy controls. All outcomes except SARA and ATXN3 were z-transformed. Z-scores of MRI volumes and FA values were inverted. For SARA, the time point, at which the score crossed the cut-off of 3 are shown. CGM = cerebellar grey matter. CWM = cerebellar white matter. FA ICP = fractional anisotropy of inferior cerebellar peduncle. FA SCP = fractional anisotropy of superior cerebellar peduncle. n.d. = not determinable. NfL = neurofilament light chain. RD ICP = radial diffusivity inferior cerebellar peduncle. SARA = Scale for the Assessment and Rating of Ataxia. SCP = superior cerebellar peduncle.

***Table 2:* Onset of abnormality of SARA, ATXN3, NfL, and MRI measures in SCA3.**

stage, the SCSs of SCP volume (0.62 [0.04–1.05]) and FA SCP (0.45 [0.17–0.92]) were larger than 0, whereas the SCSs of SARA and all other analysed biological markers did not differ from 0. In the biomarker stage, SCSs of SARA, NfL, all MRI volumes except midbrain, and RD ICP were larger than 0. In this stage, pons volume had the highest SCS of all outcome measures (1.41 [0.64–3.29]), followed by SCP (0.81 [0.34–1.64]) and CWM volume (0.78 [0.11–1.73]). Pons volume also had the highest SCS in the ataxia stage (1.71 [1.32–2.45]). It markedly exceeded the SCS of SARA (0.69 [0.60–0.80]). In the ataxia stage, the SCSs of NfL and FA SCP did not differ from 0, whereas all other biological markers had SCSs larger than 0 (Table 3).

Predictors of clinical progression

To identify factors that predicted SARA progression we applied univariable and multivariable modelling. In the univariable analysis of the entire disease, lower age, larger CAG repeat length, and lower volumes of medulla oblongata, midbrain, CGM, and SCP were associated with faster SARA progression. In the carrier stage, lower age, female sex, higher ATXN3 levels, larger CAG repeat length, and lower medulla oblongata and CWM volumes were predictors, in the ataxia stage, lower age, larger CAG repeat length, and lower medulla oblongata, midbrain and CGM volumes. In the biomarker stage, we did not find significant predictors (Appendix pp 10–11). The

Outcome measure	Entire disease	Carrier stage	Biomarker stage	Ataxia stage
Clinical				
SARA	0.99 (0.88–1.11)	0.07 (−0.25 to 0.52)	0.37 (0.19–0.59)	0.69 (0.60–0.80)
Fluid				
Mutant ATXN3	0.04 (−0.11 to 0.20)	0.09 (−0.78 to 7.61)	−0.11 (−1.55 to 0.72)	0.10 (−0.01 to 0.21)
NfL	0.21 (0.14–0.30)	0.51 (−0.11 to 1.28)	0.63 (0.37–0.99)	0.08 (−0.03 to 0.19)
MRI volume				
Medulla oblongata	0.48 (0.33–0.73)	0.20 (−0.56 to 0.60)	0.52 (0.04–1.20)	0.30 (0.13–0.75)
Pons	1.35 (1.11–1.78)	0.19 (−0.11 to 0.50)	1.41 (0.64–3.29)	1.71 (1.32–2.45)
Midbrain	0.49 (0.34–0.80)	−0.18 (−0.59 to 0.12)	0.31 (−0.17 to 0.89)	0.40 (0.16–1.00)
CWM	1.01 (0.85–1.23)	−0.03 (−0.54 to 0.22)	0.78 (0.11–1.73)	1.10 (0.84–1.48)
CGM	0.64 (0.50–0.80)	0.00 (−0.25 to 0.49)	0.48 (0.19–0.79)	0.72 (0.54–0.93)
SCP	0.69 (0.52–0.94)	0.62 (0.04–1.05)	0.81 (0.34–1.64)	0.30 (0.14–0.53)
MRI diffusion measures				
FA ICP	0.56 (0.44–0.67)	0.11 (−0.22 to 0.40)	0.24 (−0.03 to 0.58)	0.17 (0.03–0.32)
RD ICP	0.56 (0.44–0.71)	0.17 (−0.08 to 0.70)	0.51 (0.17–1.02)	0.24 (0.09–0.40)
FA SCP	0.38 (0.22–0.58)	0.45 (0.17–0.92)	0.26 (−0.06 to 0.54)	0.04 (−0.11 to 0.23)

Data are the estimated slope of progression (95% CI). CWM = cerebellar white matter. FA ICP = fractional anisotropy of inferior cerebellar peduncle. FA SCP = fractional anisotropy of superior cerebellar peduncle NfL = neurofilament light chain. RD ICP = radial diffusivity inferior cerebellar peduncle. SARA = Scale for the Assessment and Rating of Ataxia. SCP = superior cerebellar peduncle.

Table 3: **Stage-specific sensitivity to change (SCS) of SARA, ATXN3, NfL, and MRI measures in SCA3.**

multivariable analysis of the entire disease course selected lower age (p = 0.0459, slope change −0.0009 [95% CI of slope change −0.0018 to 0.0000]) and lower medulla oblongata volume (p < 0.0001, slope change −0.0208 [95% CI of slope change −0.0298 to −0.0115]) as predictors of SARA progression (Fig. 2, Appendix p 11).

Discussion

This longitudinal study determined the sequence and extent of plasma mutant ATXN3, plasma NfL and MRI outcome measure changes along the SCA3 disease course in participants of the ESMI cohort. We analysed the data in the framework of the recently proposed SCA3 staging model that distinguishes an asymptomatic carrier stage, a biomarker stage and the final ataxia stage.[16]

The present analysis showed that pre-ataxic SCA3 mutation carriers on average entered the biomarker stage 21.5 years before clinical onset with an upper margin of the 95% CI of 9.5 years before onset. The moderate difference to the previously reported time of 13.3 years is most likely due to the fact that we now analysed longitudinal data, while the previous analysis was based on cross-sectional data.[16] The ataxia stage started 4.2 years before the onset, defined by the estimated or reported onset of gait abnormalities. In the RISCA study, the observed conversion of SCA mutation carriers to ataxia also occurred before the estimated onset.[22] These data provide convergent evidence that the clinically determined ataxia onset precedes the self-

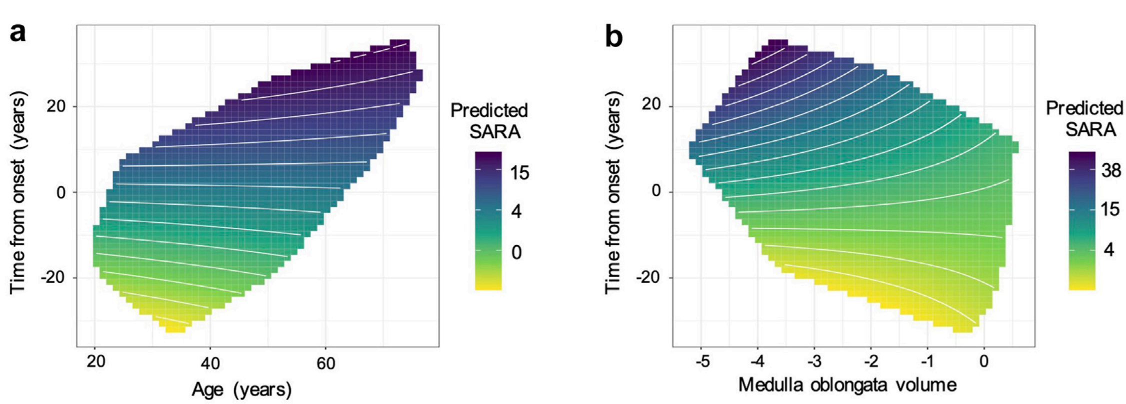

Fig. 2: Partial dependence plots of the multivariable model for SARA progression, including variables with p < 0.05 in univariable models. Predicted values of SARA as a function of the time from onset and age (a) and the time from onset and medulla oblongata volume given as z-score (b). In both panels, the value of the other predictor was set to the observed mean (medulla oblongata volume: −2.6; age: 46.4 years), respectively. The closer the white lines, which represent identical SARA values, are together, the faster is the predicted progression.

perceived onset, which is generally equated with the clinical onset. The number of observed transitions between stages was low. This reflects the relatively slow progression of SCA3. In a minority of cases, we observed counter-intuitive improvements over time which are most likely due to individual fluctuations of outcome measures. Indeed, video-based home recordings of SARA revealed short-term fluctuations of several score points.[23]

Mutant ATXN3 concentrations were almost constant across the entire disease course and did not show relevant dynamics. Correspondingly, ATXN3 provides no information about the progression of SCA3. This is in line with previous studies, where ATXN3 did not show a correlation with disease onset or severity.[4] However, ATXN3 has potential as a target engagement marker in gene silencing trials.[3,4] NfL levels became abnormal earlier than any of the analysed MRI measures. NfL slowly increased and stayed at elevated levels throughout the disease course. Like in previous studies,[9] it did not show a sensitivity to change in the ataxia stage. As NfL reflects the rate of neurodegeneration rather than disease severity, constantly increased NfL levels indicate ongoing disease progression. NfL might therefore be studied as a treatment response marker for SCA3.[5,8]

The earliest MRI abnormalities were volume loss of the medulla oblongata and reduced FA ICP, followed by volume loss of the pons and increased RD ICP, while cerebellar measures became abnormal only in the later course. The ICP contains the dorsal spinocerebellar tract and fibre tracts connecting the medulla oblongata with the cerebellum. Together with previous reports of impaired microstructural integrity of the ICP in preataxic SCA3 mutation carriers,[15,24] these findings suggest a pathological process that originates in the spinal cord and lower brainstem and further ascends to the cerebellum. They further indicate early white matter pathology in SCA3. This is in line with the observation of impaired oligodendrocyte maturation in two animal models of SCA3.[25,26]

To assess the responsiveness of SARA and the analysed biological markers, we determined the SCSs for each of them. This analysis revealed stage-dependence of SCSs. In both, biomarker and ataxia stage as well as across the entire disease course, pons volume had the highest SCS of all analysed measures. The superior responsiveness of the MRI volume measures compared to SARA is in line with previous studies in small cohorts of ataxic SCA3 individuals.[11,12] Our results agree with those of a prospective MRI study of 24 SCA3 mutation carriers over 6 months in that MRI measures were more sensitive to change than SARA and that pons volume had the highest responsiveness of the studied MRI measures.[14] The responsiveness of NfL was low across the entire disease course. This is in agreement with a previous longitudinal study in 19 SCA3 patients that did not find a NfL increase over two years.[9]

This study not only investigated the influence of biological factors, such as age, sex, and CAG repeat length, on disease progression in SCA3, but also that of fluid and MRI markers. Some, but not all previous studies in SCA3 reported an association between the length of the expanded CAG repeat and faster progression of ataxia severity.[27–30] In addition, greater CAG repeat length was reported to be a risk factor for the conversion of pre-ataxic SCA3 individuals to manifest ataxia.[22] In the univariable analysis of the present data, greater CAG repeat length and lower age were associated with faster SARA progression. In the multivariable analysis, lower age was one of two selected factors. As CAG repeat length and age of onset are inversely correlated in SCA3,[1] the opposing effects of CAG repeat length and age suggest a biological effect of the expansion size on the dynamics of disease progression. Of all biological markers investigated, only MRI volume measures were identified as predictors of progression. Among them, lower medulla oblongata volume had the most consistent effect.

A main limitation of this study is the small number of observed stage transitions. We were therefore not in the position to identify predictors of progression, as indicated by transition to more advanced disease stages. Another limitation is that the study was conducted mainly with European participants. It is thus unclear, whether the results can be generalised to SCA3 mutation carriers from other world regions.

In conclusion, our study provides quantitative information on the progression of biological markers in SCA3 mutation carriers before and after onset of ataxia, and allowed the identification of predictors for clinical progression. Our data are useful for the design of future clinical trials. Of particular importance is the finding that pons volume was more sensitive to change than any other outcome. This characterises pons volume as a useful marker to monitor progression in clinical trials.

Contributors

Conceptualisation: JF, TK, MB. *Data curation, formal analysis*: JF, MB, MF, HGM, JHS, TS, PW, TE, KT, MSch. *Methodology, Resources, validation and visualisation*: MB, JF, MF, HGM, PG, JHS. *Writing—original draft*: JF, TK, MB, MF, HGM, JHS, TS. *Investigation*: JF, TK, ML, LPdA, PG, BvdW, JdV, JI, GO, OR, LS, KR, DT, JS, CO, HJ, MMS, JHS, JvG, THvP, CGR, SK, AH, HZ, MR, AFF, JV, ALP, LMq, ID, JMJo, KB, MPov, EMR, MSy. *Project administration*: TK, JF, ML, LPdA, PG, BvdW, JdV, JI, GO, OR, LS, KR, DT, JS, CO, HJ, MMS, JHS. *Writing—review & editing*: ML, LPdA, PG, BvdW, JdV, JI, GO, OR, LS, KR, DT, JS, CO, HJ, MMS, PW, TE, KT, MSch, JvG, THvP, CGR, SK, AH, HZ, MR, AFF, JV, ALP, LMq, ID, JMJo, KB, MPov, EMR, MSy. *Funding acquisition*: TK, JF, GO, BvdW, OR, LS, ML, LPdA, PG.

JF, TK, MB, MF, JHS, HGM verified the data and had access to the raw data. JF, TK, MB, PG, MF, JHS and HGM had the final responsibility for the decision to submit for publication.

Data sharing statement

The data are not publicly available but can be accessed upon reasonable request to the consortium, subject to approval.

Declaration of interests

JF received consultancy honoraria from Vico therapeutics, unrelated to the present manuscript. GO has consulted for IXICO Technologies Limited, Servier and UCB Biopharma SRL/Lacerta Therapeutics Inc, serves on the Scientific Advisory Board of BrainSpec Inc. and received research support from Biogen, each unrelated to the current manuscript. JS is site PI for Biohaven Pharmaceuticals clinical trials NCT03701399 and NCT02960893; received consults for Biohaven Pharmaceuticals; and royalties from Oxford University Press, Elsevier, MacKeith Press, and Springer; and is the inventor of the Brief Ataxia Rating Scale, Cerebellar Cognitive Affective/Schmahmann Syndrome Scale, the Patient Reported Outcome Measure of Ataxia, and the Cerebellar Neuropsychiatry Rating Scale which are licenced to the General Hospital Corporation; all unrelated to the current manuscript. MGE received consultancy honoraria from Biogen and Healthcare Manufaktur Germany, both unrelated to the present manuscript. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave. HZ is chair of the Alzheimer's Association Global Biomarker Standardization Consortium and chair of the IFCC WG-BND. HZ is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and a shareholder of MicThera (outside submitted work). PG has received grants and honoraria for advisory board from Vico Therapeutics, honoraria for advisory board from Triplet Therapeutics, grants and personal fees from Reata Pharmaceutical, grants from Wave. LS has received consultancy honoraria from Vico, Alexion and Novartis, unrelated to the present manuscript. MSy has received consultancy honoraria from Ionis, UCB, Prevail, Orphazyme, Biogen, Servier, Reata, GenOrph, AviadoBio, Biohaven, Zevra, Lilly, Quince, and Solaxa, all unrelated to the present manuscript. TK received consultancy honoraria from Arrowhead, Bristol Myers Squibb and UCB, unrelated to the present manuscript. KR received consultancy honoraria from Roche and Lilly unrelated to the present manuscript. BvdW would like to thank Heidi van den Boogaard and Janneke Rigter-Schimmel for their help in the ESMI logistics and assessments. JAR received honoraria for participation in advisory boards and speaking fees for Roche, Novartis Gene therapy and Biogen, all in the field of paediatric neuromuscular disorders. IC has received honoraria for participation in advisory boards and speaking fees for Bial, in the field of Epilepsy. AT holds stocks of Viatris Inc. is a pharmaceutical company. EMR received consulting fees from Aletheia and is part of the advisory board of Brain Spec without financial support. We would like to thank Anne Boehlen for her support in the administration of ESMI.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101339.

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