Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study


Summary

Background Spinocerebellar ataxias are dominantly inherited neurodegenerative diseases. As potential treatments for these diseases are being developed, precise knowledge of their natural history is needed. We aimed to study the long-term disease progression of the most common spinocerebellar ataxias: SCA1, SCA2, SCA3, and SCA6. Furthermore, we aimed to establish the order and occurrence of non-ataxia symptoms, and identify predictors of disease progression.

Methods In this longitudinal cohort study (EUROSCA), we enrolled men and women with positive genetic testing for SCA1, SCA2, SCA3, or SCA6 and with progressive, otherwise unexplained ataxia who were aged 18 years or older from 17 ataxia referral centres in ten European countries. Patients were seen every year for 3 years, and at irregular intervals thereafter. The primary outcome was the scale for the assessment and rating of ataxia (SARA), and the inventory of non-ataxia signs (INAS). We used linear mixed models to analyse progression. To account for dropouts, we applied a pattern-mixture model. This study is registered with ClinicalTrials.gov, number NCT02440763.

Findings Between July 1, 2005, and Aug 31, 2006, 526 patients with SCA1, SCA2, SCA3, or SCA6 were enrolled. We analysed data for 462 patients with at least one follow-up visit. Median observation time was 49 months (IQR 35–72). SARA progression data were best fitted with a linear model in all genotypes. Annual SARA score increase was 2·11 (SE 0·07) in patients with SCA1, 1·49 (0·07) in patients with SCA2, 1·56 (0·08) in patients with SCA3, and 0·80 (0·09) in patients with SCA6. The increase of the number of non-ataxia signs reached a plateau in SCA1, SCA2, and SCA3. In patients with SCA6, the number of non-ataxia symptoms increased linearly, but more slowly than in patients with SCA1, SCA2, and SCA3 (p<0·0001). Factors that were associated with faster progression of the SARA score were short duration of follow-up (p=0·0179), older age at inclusion (0·04 [SE 0·02] per additional year; p=0·0476), and longer repeat expansions (0·06 [SE 0·02] per additional repeat unit; p=0·0128) in SCA1, short duration of follow-up (p=0·0001), lower age at onset (–0·02 [SE 0·01] per additional year; p=0·0014), and lower baseline SARA score (–0·02 [SE 0·01] per additional SARA point; p=0·0083) in SCA2, and lower baseline SARA score (–0·01 [SE 0·01] per additional SARA point; p=0·0195) in SCA6. In SCA3, we did not identify factors that affected progression of the SARA score.

Interpretation Our study provides quantitative data on the progression of the most common spinocerebellar ataxias based on a follow-up period that exceeds those of previous studies. Our data could prove useful for sample size calculation and patient stratification in interventional trials.

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Introduction

The spinocerebellar ataxias are autosomal, dominantly inherited progressive ataxia disorders. More than 35 genetically different types of spinocerebellar ataxia have been defined. The most common, SCA1, SCA2, SCA3, and SCA6, which together affect more than half of all families with dominantly inherited ataxia, are caused by translated polyglutamine tracts within the proteins associated with each type. Clinically, they are characterised by progressive unsteadiness of gait and stance, impaired coordination of limb movements, slurred speech, and abnormal eye movements with an onset usually in adult life. These symptoms are the result of cerebellar degeneration that is typically accompanied by degeneration of other parts of the CNS and peripheral nervous system in SCA1, SCA2, and SCA3, but not in SCA6. In SCA1, SCA2, and SCA3, ataxia typically manifests in the fourth decade of life, whereas the onset of ataxia in SCA6 is about 20 years later. In all four genotypes, the age of ataxia onset is inversely associated with the length of the expanded allele.¹

As potential treatments for spinocerebellar ataxias are being developed, the natural history needs to be characterised by assessing the functional decline in each type and to identify factors that determine disease progression. To address these issues, in 2005 we initiated
Evidence before this study
We searched PubMed with the search terms [“spinocerebellar ataxia” OR “SCA” OR “dominant ataxia” OR “Machado-Joseph disease” AND “natural history” OR “progression”] for reports published before May 31, 2015. Only peer-reviewed, English language reports were considered. We included longitudinal studies reporting disease progression, as established by semi-quantitative rating scales. In our search we identified seven studies. One study is an interim analysis of the 2-year follow-up data of this cohort. Three studies were restricted to a single genotype (SCA3 or SCA6) precluding a comparison between different genotypes. Three studies included the most common spinocerebellar ataxia genotypes, but observation times and case numbers were small. None of these studies specifically considered symptoms other than ataxia.

Added value of this study
In this European, multicentre, longitudinal study (EUROSCA), we studied a large cohort of patients with SCA1, SCA2, SCA3, or SCA6 for up to 8 years. We noted a linear progression of the Scale for the Assessment and Rating of Ataxia score in all genotypes, whereas the number of non-ataxia symptoms reached a plateau in SCA1, SCA2, and SCA3. Genotypes differed with respect to the rate of progression. Longer repeat expansions and lower age of ataxia onset were associated with faster progression in SCA1 and SCA2, and women with SCA3.

Implications of all the available evidence
Our data have substantial implications for the design of future interventional studies of SCA1, SCA2, SCA3, and SCA6 because they allow sample size calculations for each genotype and provide a basis for patient stratification. Additionally, they emphasize the usefulness of the scale for the assessment and rating of ataxia as a clinical outcome parameter.

Methods
Study design and participants
In this longitudinal cohort study, we enrolled patients with SCA1, SCA2, SCA3, or SCA6 at 17 European ataxia referral centres. Patients were identified with the help of an electronic patient registry that contained data for all patients determined at the Institute of Medical Genetics and Applied Genomics of the University of Tübingen (Tübingen, Germany).

Panel: Research in context

The EUROSCA natural history study, a European multicentre longitudinal cohort study of patients with SCA1, SCA2, SCA3, or SCA6. At baseline, we recorded phenotypical differences between the genotypes and identified factors that determined disease severity. A first analysis of longitudinal data after 2 years allowed us to establish genotype-specific progression rates. In this study, we report longitudinal data from the EUROSCA cohort based on an 8-year observational period. The aim of this study is to model the long-term disease progression of SCA1, SCA2, SCA3, and SCA6, and to identify factors that determine the disease course.

Statistical analysis
To investigate whether baseline characteristics of patients who had been followed up only for the initial 3 years (plus or minus 3 months) period differed from those of patients who had been followed longer, we used t tests for quantitative and χ² tests for categorical variables. For analysis of disease progression, we applied a linear mixed model with random effects on intercept and slope. The time variable was the year since inclusion. Linearity of the progression rate was tested via nested models (likelihood ratio test). Specifically, we tested for a linear
and quadratic effect of time and chose the model that best fitted the data. Because the progression rate differed between patients who had been followed up only for the initial 3 years (plus or minus 3 months) and those who had been followed up for longer, we used a pattern-mixture model to obtain an unbiased estimation of progression. For comparison of the progression rates between the genotypes, we adjusted the pattern-mixture model according to the genotype in addition to the duration of follow-up.

To identify factors that affected disease progression, we added the tested factor in interaction with the linear mixed model used for analysis of disease progression taking into account the missing data model of progression. The tested factors were the baseline SARA score, the number of non-ataxia signs at baseline, and sex, age at onset, age at inclusion, disease duration, repeat length of the expanded allele, and repeat length of the normal allele. We tested the effect of these variables on the progression rate via interactions between the given factor and the time variable. Independent factors that were significant in the univariate analysis were included in a multivariable model, including the interactions with backward selection. Estimates derived from the model are given as mean and standard error. We eliminated values of three patients with SCA6 with extreme outliers of the SARA score at one visit. These outliers were identified by visual inspection of the residual graphs and then going back to the raw data of the patients. Data were excluded when the SARA score was not consistent with concurrent disease not related to ataxia as a cause of discrepant performance in SARA.

We used SAS (version 9.3) for statistical analyses; all tests were two-sided. Test results were deemed as significant at the 0.05 level. Bonferroni correction was used for comparison of disease progression between genotypes.

This study is registered with ClinicalTrials.gov, number NCT02440763.

Role of the funding source

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

Results

Between July 1, 2005, and Aug 31, 2006, we enrolled 526 patients with SCA1, SCA2, SCA3, or SCA6. We did analyses in a subgroup of 462 patients (107 with SCA1, 146 with SCA2, 122 with SCA3, and 87 with SCA6) who had at least one follow-up visit. The table shows demographic and clinical data. Although disease duration and baseline SARA scores were similar in all genotypes, patients with SCA6 had an older age at inclusion, older age of onset, and lower number of non-ataxia signs at baseline than patients with other genotypes. 2192 visits were analysed. Patients had a median of five (IQR 4–6) visits and a median observation duration of follow-up.

Table: Cohort characteristics at baseline

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Men (%)</th>
<th>Age (years)</th>
<th>Age at onset (years)</th>
<th>Disease duration (years)</th>
<th>Length of expanded allele (repeat units)</th>
<th>Length of normal allele (repeat units)</th>
<th>SARA score</th>
<th>Number of non-ataxia signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>66 (62%)</td>
<td>46 (12)</td>
<td>37 (11)</td>
<td>9 (5)</td>
<td>49 (6)</td>
<td>30 (2)</td>
<td>14 (8.4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>SCA2</td>
<td>68 (47%)</td>
<td>46 (14)</td>
<td>35 (13)</td>
<td>11 (6)</td>
<td>40 (4)</td>
<td>22 (1)</td>
<td>15 (7.7)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>SCA3</td>
<td>61 (50%)</td>
<td>50 (12)</td>
<td>38 (11)</td>
<td>12 (6)</td>
<td>71 (4)</td>
<td>22 (1)</td>
<td>14 (7.8)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>SCA6</td>
<td>48 (55%)</td>
<td>65 (11)</td>
<td>55 (10)</td>
<td>10 (6)</td>
<td>10 (6)</td>
<td>12 (1)</td>
<td>15 (7.9)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%). SARA=Scale for the Assessment and Rating of Ataxia. SCA=spinocerebellar ataxia.

Figure 1: Progression of SARA scores in SCA1 (A), SCA2 (B), SCA3 (C), and SCA6 (D)

Data are mean (95% CI). Red, black, and blue dots indicate the mean values. Continuous black lines show the recorded values of all patients of one genotype. In SCA1 and SCA2, the blue curve represents the recorded values of participants with a follow-up of up to 3 years (plus or minus 3 months), and the red curve participants with a longer follow-up. Because there was no difference in SCA1 and SCA6 between patients with the shorter and longer follow-up, only the recorded values of all patients are shown for these genotypes. The dashed curves show the estimated progression taking into account missing data by pattern-mixture modelling. SARA=Scale for the Assessment and Rating of Ataxia. SCA=spinocerebellar ataxia.
time of 49 months (IQR 35–72). 415 patients were seen for a follow-up visit after 1 year, 416 after 2 years, and 336 after 3 years. 1094 (94%) of these follow-up visits were done within the planned time window of 3 months around the scheduled time. The appendix shows flowcharts detailing the number of patients seen in each year and reasons for dropout.

First, we compared patients who had been followed up only for the initial 3 years (plus or minus 3 months) with those who had been followed up for longer. We noted no group differences in sex, age at onset, age at inclusion, and repeat length (appendix). However, in patients who had shorter follow-up, disease duration was longer in those with SCA1 or SCA2 (SCA1 10.7 years [SD 5.7] vs 7.7 [4.5], p=0.0026; SCA2 12.9 [5.8] vs 9.9 [6.0], p=0.0039), baseline SARA scores were higher in those with SCA1, SCA2, and SCA3 (SCA1 17.4 [9.6] vs 12.3 [6.4], p=0.0021; SCA2 17.4 [8.4] vs 14.5 [7.0], p=0.0254; SCA3 16.4 [8.3] vs 12.5 [7.0], p=0.0067), and the number of non-ataxia signs at baseline was higher in those with SCA1 or SCA3 (SCA1 5.3 [2.5] vs 4.3 [1.8], p=0.0259; SCA3 5.4 [2.6] vs 4.3 [2.1], p=0.0210) than those with longer follow up. Additionally, for patients with SCA1, SCA2, or SCA3, patients who had shorter follow-up were more likely to drop out for disease-related reasons or death than those with longer follow-up (SCA1: 20 [38.5%] vs 11 [20.0%]; p=0.0017; SCA2: 28 (46.7%) vs seven (8.1%; p=0.0001; SCA3: 14 (28.0%) vs nine (12.5%; p=0.0015; appendix). P values refer to comparison of the reason for stopping according to duration of follow-up for each genotype.

SARA progression data were best fitted with a linear model in all genotypes. In patients with SCA1 or SCA2, disease progression was faster in those with a maximum follow-up of 3 years (plus or minus 3 months) than in those with a longer follow-up. To account for this, we applied a pattern-mixture model that allowed us to calculate a mean annual progression in SARA score of 2.11 (SE 0.12) in patients with SCA1 and 1.49 (0.07) in patients with SCA2. In SCA3, the progression was 1.56 (0.08) and in SCA6 was 0.80 (0.09; figure 1). SARA progression differed between genotypes (p<0.0001). Pairwise comparisons showed differences between SCA1 and SCA2 (p<0.0001), SCA1 and SCA3 (p=0.0002), SCA1 and SCA6 (p<0.0001), SCA2 and SCA6 (p<0.0001), and SCA3 and SCA6 (p<0.0001), but not between SCA2 and SCA3 (p=0.049; p=0.0083 threshold with Bonferroni) and that SARA progression was fastest in SCA1, intermediate in SCA2 and SCA3, and slowest in SCA6 (figure 1).

Based on the progression of the SARA score, we calculated sample sizes needed for two-group interventional trials of 1 year duration in each genotype (figure 2). Estimated sample sizes per group to achieve 80% and 90% power with effect sizes ranging from 20% to 100% are shown in figure 2. In SCA1, a trial with 142 patients (71 per group) would be able to detect a 50% reduction in progression of the SARA score. The corresponding patient numbers for SCA2, SCA3, and SCA6 are 172, 202, and 602, respectively. In a 2-year trial, 72 patients would be needed for SCA1, 88 for SCA2, 102 for SCA3, and 302 for SCA6; and in a 3-year trial, 50 would be needed for SCA1, 60 for SCA2, 70 for SCA3, and 202 for SCA6.

To identify factors that were independently associated with faster progression of the SARA score we applied multivariable modelling. In patients with SCA1, we found that short duration of follow-up (3 years plus or minus 3 months; p=0.0179), older age at inclusion (0.04 [SE 0.02] per additional year; p=0.0476), and longer repeat expansions (0.06 [0.02] per additional repeat unit; p=0.0128) were associated with faster progression. The corresponding factors in SCA2 were short duration of follow-up (p=0.0001), lower age at onset (–0.02 [0.01] per additional year; p=0.0014), and lower baseline SARA score (–0.02 [0.01] per additional SARA point; p=0.0083). In SCA6, a lower SARA score at baseline was associated with faster disease progression (–0.03 [0.01] per additional SARA point; p=0.0195), whereas we did not identify factors associated with SARA progression in SCA3 (appendix).

The increase of the number of non-ataxia signs was linear only in SCA6, whereas it was attenuated and reached a plateau towards the end of the observation period in SCA1, SCA2, and SCA3 (figure 3). The increase of the number of non-ataxia signs was different between genotypes (p<0.0001). It did not differ between SCA1, SCA2, and SCA3, but each of these genotypes had a faster increase of the number of non-ataxia signs than SCA6 (p=0.0001; p value for pairwise comparisons of SCA1 vs SCA6, SCA2 vs SCA6, and SCA3 vs SCA6; p<0.0042 threshold with Bonferroni correction).
In patients with SCA3, the increase of the number of non-ataxia signs was faster in women than in men (figure 3C and D; p=0.0312), whereas we did not find differences between men and women in the other genotypes. Lower age of onset was an independent factor associated with faster increase of the number of non-ataxia signs in patients with SCA1 (–0.07 [SE 0.03] per additional year; p=0.0192), SCA2 (–0.11 [0.02] per additional non-ataxia sign; p=0.0001), or SCA6 (–0.08 [0.02] per additional non-ataxia sign; p=0.0025; appendix).

To find out what non-ataxia signs appeared earlier in the disease course, we compared the frequency of each non-ataxia sign at the 3 year follow-up visit with that at baseline (appendix). In patients with SCA1, the frequency of paresis, muscular atrophy, sensory symptoms, urinary dysfunction, and brainstem oculomotor signs increased. In patients with SCA2, the frequency of areflexia, spasticity, resting tremor, sensory symptoms, urinary dysfunction, and brainstem oculomotor signs increased. In patients with SCA3, the frequency of paresis and brainstem oculomotor signs increased. In patients with SCA6, none of the signs increased in frequency.

Discussion
This study provides quantitative data for the disease progression of SCA1, SCA2, SCA3, and SCA6 based on 8 year longitudinal findings from the EUROSCA cohort. Strengths of our study include the large number of patients and the observational period of up to 8 years. On average, patients were enrolled around 10 years after disease onset. In view of the estimated survival times of individuals with spinocerebellar ataxia (about 20–25 years from onset of ataxia),7 many of the patients progressed to severe disability or died during the course of the study. Consequently, there was a substantial dropout mainly because of disease-related reasons in the open extension period that followed the initial 3 year period with annual visits. The dropout rate was especially high in those who had a longer disease duration (ie, patients with SCA1 or SCA2) and greater disease severity (ie, patients with SCA1, SCA2, or SCA3) at baseline. In patients with SCA1 and SCA2, individuals with a maximum follow-up of 3 years showed a faster disease progression than those who stayed longer in the study, which suggested that those with a maximum follow-up of 3 years represented participants with a worse disease course. To handle missing data and estimate disease progression in an unbiased way, we applied a pattern-mixture model approach. Pattern mixture models consider missing data as a random process, with the distribution depending on the other recorded information. Therefore, the average progression is estimated as the weighted mean of the progression in the group with a follow-up of up to 3 years and the progression in the group with extended follow-up.6 Although statistical measures were taken to handle missing data, the dropout resulting in few patients being seen at the final visits is a limitation of this study.
Another limitation is the restriction to clinical assessment and the absence of long-term imaging data.

We used SARA as the primary outcome parameter, a clinical scale that is based on a semi-quantitative assessment of cerebellar ataxia on an impairment level. SARA underwent a rigorous validation procedure involving several trials in large groups of patients with ataxia and controls. Although ataxia is the main and most disabling symptom in most patients with spinocerebellar ataxia, many have additional non-ataxia symptoms. To assess these symptoms, we used INAS, which yields the number of non-ataxia signs as a measure of neurological involvement apart from ataxia. Other scales that allow a comprehensive assessment of non-ataxia symptoms are currently not available. Both measures, the SARA score and the number of non-ataxia signs, are major determinants of health-related quality of life in individuals with spinocerebellar ataxia. Changes in SARA reflect the patient’s perception of change in disease status. Compared with SARA, the number of non-ataxia signs is less sensitive to change. The reason might lie in scale properties, but also in biological characteristics of spinocerebellar ataxias, which are clinically characterised by prominent ataxia.

Progression of ataxia as measured by the SARA score was best fitted with a linear model in all four genotypes studied. We noted that lower SARA scores at baseline were associated with faster progression in SCA2 and SCA6, suggesting that a more complex model might provide a better fit. However, a quadratic model and thus a plateau effect was excluded for these two genotypes. By contrast, the results of the analysis of this cohort after 2 years showed a non-linear SARA progression in SCA6. This discrepancy highlights the importance of sufficiently long observation periods in natural history studies of progressive disorders. Linearity of SARA progression suggests that the neurodegeneration underlying the development of ataxia in SCA1, SCA2, SCA3, and SCA6 is a steady process continued over an extended time period. By contrast, the increase of the number of non-ataxia signs in SCA1, SCA2, and SCA3 reached a plateau during the observation period. Most probably because of the short observation time, we did not note an attenuation during the observation period. By contrast, the increase of the number of non-ataxia signs might serve as a rough semi-quantitative measure of non-cerebellar involvement in spinocerebellar ataxias, further increases in the severity of any of these symptoms are not captured by this measure, but would need additional quantitative assessment. Nevertheless, the different pattern of progression of non-ataxia signs in SCA6 compared with SCA1, SCA2, and SCA3 is indicative of the paucity of extracerebellar degeneration in SCA6.

Progression of ataxia was fastest in SCA1 followed by SCA2 and SCA3, between which progression rates did not differ, and SCA6, which had the slowest progression. Findings of a US prospective study showed that disease progression in SCA1 was faster than that in SCA2, SCA3, and SCA6, but 2 year follow-up data were available for only 14 of 345 patients. In a Taiwanese study that recorded the SARA score in a small cohort of patients with SCA2, SCA3, and SCA6 over 8 to 38 months, patients with SCA2 and SCA3 progressed at almost the same rate, whereas the increase of the SARA score in SCA6 was slower. However, the overall rate of progression in this study was much larger than in our cohort. Likewise, a Japanese study that combined retrospective and prospective data of 46 patients with SCA6 reported a faster SARA progression than we recorded.

In a study of 34 Brazilian patients with SCA3, the score of the International Cooperative Ataxia Rating Scale (ICARS) increased by 5·1 points over an observation period of 13 months. If this change is related to the baseline ataxia score, the annual progression rate was 12%, which was similar to the rate noted in our study (11%). In a large cohort of Brazilian patients with SCA3 followed up for 5 years, the neurological examination score for spinocerebellar ataxia (NESSCA) increased by 1·26 per year. Although this score has the same range as SARA, a direct comparison is not possible because NESSCA jointly considers ataxia and non-ataxia signs.

Although our results are largely consistent with those of previously published cohorts, the progression was slower than in the Taiwanese and Japanese cohorts. This can be partly explained by the longer follow-up period in our study. In our cohort, patients with SCA1 and SCA2 with a follow-up beyond the initial 3 year observation period showed slower progression than those with a shorter follow-up. Because observation times in previous studies were shorter, disease progression might have been faster. Additionally, the different ethnic background of the Taiwanese and Japanese cohorts compared with our European cohort might have contributed to the discrepant findings.

Our data allow the calculation of genotype-specific sample sizes required for interventional trials. Our calculation showed that in SCA1, SCA2, and SCA3, 142 to 202 patients would be needed to detect a 50% reduction in progression of the SARA score in a 1 year trial. These numbers can be reduced by doing trials of 2 or 3 year duration. However, longer study durations are typically associated with higher dropout rates. In our study dropout was moderate within the first 3 years and
substantially increased thereafter. This finding is in accordance with previous calculations in these genotypes that were based on much smaller groups and shorter observation periods. Because of the slower progression of SCA6, estimated sample sizes in this genotype are much larger, making interventional trials aimed at slowing disease progression in SCA6 very challenging.

Factors associated with fast SARA progression included longer repeat expansions in SCA1 and lower age at onset in SCA2. Additionally, young age of onset was associated with fast increase in the number of non-ataxia symptoms in patients with SCA1, patients with SCA2, and in women with SCA3. Because there is a close inverse correlation between repeat length and age of onset, these findings suggest a biological effect of the expansion size on the dynamics of disease progression. In SCA3, one study did not show an accelerating effect of repeat length on progression of ataxia as measured by the ICARS, whereas another study did report an effect on progression of the NESSCA score. Because NESSCA assesses severity of both ataxia and of non-ataxia signs, the results of these cohorts are compatible with the present finding that lower age at onset was associated with a faster increase of non-ataxia signs, but not of the SARA score in women with SCA3. In patients with SCA6, we did not find an effect of CAG repeat length or age of onset on disease progression, thereby confirming negative results of a previous Japanese SCA6 cohort study. The absence of effect of CAG repeat length or age of onset on progression in SCA6 is unexpected because longer repeats are associated with earlier disease in SCA6, similar to SCA1, SCA2, and SCA3. Possible reasons for this finding are the small variation of the repeat length and the slower disease progression in SCA6.

Our data have important implications for the understanding of the biological characteristics of disease progression in SCA1, SCA2, SCA3, and SCA6. Furthermore, our study provides useful information for counselling of patients and the design of interventional trials in these disorders, in particular of trials that test interventions aimed at modifying the disease course.

Contributors
HJ and TS-H contributed to the concept, organisation, and execution of the research project and reviewed and commented on the statistical analysis and the report; StG reports grants from the European Union (EU) during the conduct of the study; PB received consultancy and speakers honoraria from Actelion and Cento-gene, and patent royalties from Roche, and received funding from the German Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF; e-rare EUROSCAR JTC 2001 01G1206) and the European Commission (EC, Neuronomics FP7-HEALTH-30512) and ASv received research funding from the Polish Ministry of Scientific Research and Information Technology (grant number 3 POSB 019 24) and Polish Ministry of Science and Higher Education (grant number 674—RISCA/2010). ASv reports grants from the Polish Ministry of Science and Higher Education (grant number 674-N-RISCA/2010-2014) outside the submitted work; TS-H received grants from the EU, Deutsche Forschungsgemeinschaft, Bundesministerium für Wirtschaft und Energie, and travel grants from Merz and Ipsen; LS received funding from the Deutsche Forschungsgemeinschaft (DFG, grant SCH0754/5-2), BMBF (e-rare EUROSCAR 08GM1206 and mbitoNET 01G1113E), and the European Commission (EC, Neuronomics FP7-HEALTH-30512); BPvD’W reports grants from BBMRI-NL, grants from Gossweiler Foundation, grants from Radboud University Medical Center, grants from Princes Beatrix Fonds, grants from Netherlands Brain Foundation, outside the submitted work; J-SK has received honoraria from GlaxoSmithKline, Ipsen, Merz Pharmaceuticals, Medtronic GmbH and Teva Pharmaceutical Industries; JBS serves on scientific advisory boards for Lundbeck, TEVA, Novartis, and Lilly and has received funding for travel and speaker honoraria from GlaxoSmithKline, Merz Pharmaceuticals, Medical Tribune, Lundbeck, Pfizer, Boehringer, and Bayer, and has received research support from the BMBF and the EU; TK has received research support from DFG, BMBF, and the Robert Bosch Stiftung and the EU. He receives royalties for book publications from Thieme, Urban and Schwarzenberg, Kohlhammer, Elsevier, Wissenschaftliche Verlagsgesellschaft Stuttgart and M Dekker; PG is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre and the European Commission’s Seventh Framework Programme (FP7/2007-2013) under grant agreement number 2012-305121 "Integrated European –omics research project for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases (NEUROMICS)". We thank Thomas Klopstock (Department of Neurology, University of Munich, Munich, Germany) and Jens Petersen (Department of Neurology, University of Munich, Munich, Germany) and Catherine Delnooz (Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands) and Rafal Rola (First Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland) for contributions of patients and help in patient assessment.

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finding is not explained by the relatively low doses of TEV-48125 chosen for these trials because no clear additional benefit was found with the highest dose in either trial.\(^1,6\) This apparent insufficient efficacy of CGRP antibodies in some patients could have several reasons. One obvious explanation would be that diagnosis of chronic migraine, a disorder for which diagnosis is subjective because it is based on clinical criteria only, cannot always be correct. Another potential explanation could be a role of other pain-producing molecules in migraine pain. Although CGRP released by the afferent arm of the trigemino-vascular system has a crucial role in migraine pain chronification, other molecules also contribute to migraine-pain pathophysiology, including vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide, which are released by the parasympathetic efferent arm of this system, and glutamate. To block CGRP, therefore, would be insufficient for some patients for whom other molecules cause migraine pain, whereas CGRP antibodies would be ideal for patients whose migraine pain greatly depends on this peptide, which would easily explain the subset of patients in all trials for whom CGRP antibodies elicited an excellent response. In future trials, efficacy findings should be correlated with blood levels of biomarkers, such as CGRP or VIP, which are consistently elevated in patients with migraine, especially chronic migraine.\(^7,8\)

Despite excellent short-term tolerability of TEV-48125, some further points concerning long-term safety need to be clarified in future prospective trials lasting at least 1 year. Antibodies are large molecules with limited possibility to cross the blood-brain barrier, but whether this barrier remains intact during the headaches is a topic of discussion.\(^9\) The long half-life of these compounds could potentially induce central or systemic adverse events. Furthermore, potential long-term development of autoantibodies against CGRP antibodies should be studied.

All available data point to CGRP antibodies as a step forward in migraine prevention, with potential advantages in tolerability and treatment adherence. However, the characteristics of responders to these antibodies, their ideal dose, and their long-term neurological and systemic safety must be refined.

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I have served as a consultant and participated in advisory board meetings for Allergan.


An insight into the natural history of spinocerebellar ataxias

The spinocerebellar ataxias are a genetically and clinically heterogeneous group of progressive diseases inherited as autosomal dominant disorders. The most common of these ataxias are SCA1, SCA2, SCA3, and SCA6, which are caused by pathological expansion of CAG trinucleotide repeats in the coding region and thus are referred to as polyglutaminopathies. Unfortunately, no effective treatments are available for these disorders.\(^1\) Studies of natural history of the spinocerebellar ataxias represent a key approach to assess the progression of these disorders, as they enable investigators to recognise the main determinants of
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The objective of the study was to model disease progression of SCA1, SCA2, SCA3, and SCA6, and identify factors affecting progression. The study was done between 2005 and 2013; investigators enrolled 526 patients with SCA1, SCA2, SCA3, and SCA6, of whom 462 had at least one follow-up visit. Patients were assessed once a year during the first 3 years of the study and irregularly during the remaining 5 years. As outcome measures, researchers applied the Scale for the Assessment and Rating of Ataxia (SARA) and the Inventory of Non-Ataxia Symptoms (INAS). Both clinical scales have been designed and validated by the EUROSCA consortium to semi-quantitatively measure the severity of cerebellar and non-cerebellar features, respectively. The most relevant features of this research are long follow-up time, large sample size, and inclusion of participants with the more frequent SCA subtypes.

The study’s main finding was that the progression of SARA score across time follows a linear pattern in all genotypes. The progression was fastest in patients with SCA1, with an annual progression of 2.11 (SE 0.12). Investigators noted an intermediate progression rate of 1.49 (0.07) per year in patients with SCA2 and 1.56 (0.08) in patients with SCA3, whereas in patients with SCA6 the rate of progression was slowest at 0.80 (0.09). Age at inclusion and expanded CAG repeats were identified as the main determinants of the SARA score progression in SCA1, whereas in SCA2, the progression was affected by the age at disease onset. This study will probably have a large effect on the planning and implementation of future interventional trials in spinocerebellar ataxias because it allows sample size calculations for each genotype based on progression of the SARA score and offers insights to enable better patient classification according the disease stage. A problem in the design of clinical trials is the definition of a good primary outcome parameter. After a clinical trial in spinocerebellar ataxias, researchers hope to improve the main clinical manifestations, and even to achieve a stabilisation of cerebellar features in these progressive neurodegenerative disorders. Therefore, the knowledge of magnitude of change of the SARA score is valuable.

The frequency of non-cerebellar features was different between spinocerebellar ataxias, and its progression showed a plateau in SCA1, SCA2, and SCA3. Nevertheless, INAS assessments in the context of natural history studies could be crucial in the identification of distinctive non-cerebellar features for some subtypes, such as saccade slowing in SCA2. Such differences in non-ataxia signs could be quantitated with other methods and associated with the SARA as the standard clinical measure of disease progression.

Despite the validity of these findings, it would have been important to analyse the association between the progression of SARA score and imaging findings through time, to assess the effects of morphological and pathophysiological features on disease progression. Still, this study increases understanding of the large clinical, genetic, and pathological heterogeneity of spinocerebellar progression and to identify and validate quantifiable biomarkers that can serve as outcome measures for clinical trials. In The Lancet Neurology, a group of researchers from the EUROSCA consortium led by Thomas Klockgether present the results of an extensive 8-year longitudinal study of cerebellar and non-cerebellar features of individuals with spinocerebellar ataxia, broadening the short list of prospective natural history studies in these disorders (table).
ataxias and marks an important step forward in the临床 research of these disorders. Furthermore, it could lead to improved characterisation of prodromal stages and the development of biomarkers. The findings obtained by the EUROSCA consortium reflect the value of scientific collaboration for the development of high-impact studies and could therefore be taken as a model for multinational networks in other regions such as the Americas.

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I declare no competing interests.

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Progress in autism and related disorders of brain development

In recent years, rapid advances in genetics and neuroimaging have enabled researchers to begin to unravel the mysteries of autism spectrum disorders (ASDs). As reviewed comprehensively in The Lancet Neurology,1,2 many genomic copy number variants are being found in close association with ASD,3 and variations in brain structure and connectivity, which are often subtle and need to be assessed by quantitative techniques, are providing intriguing clues to the anatomical and functional bases of the behavioural features that are characteristic of autism.2 However, major breakthroughs with clear therapeutic implications are still needed.

Recent changes to the American Psychiatric Association’s diagnostic criteria, published in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5),3 have combined previously separate diagnoses of pervasive developmental disorder not otherwise specified, autistic disorder, Asperger’s syndrome, and childhood disintegrative disorder into the single category of ASD. These conditions are now construed as a spectrum that largely reflects the severity of the behavioural manifestations of ASD and their consequences. Although this approach might be useful for obtaining the help of special services for affected individuals, we suspect that the underlying factors responsible for ASDs—whether construed as a spectrum or as discrete diagnoses—are not homogeneous. We argue that studying all ASDs as an undifferentiated entity will probably obscure important genetic heterogeneity in pathways that are being investigated for three other groups of disorders that are related to each other and to autism: intellectual disabilities, the epilepsies, and brain malformations (particularly agenesis of the corpus callosum, cerebellar hypoplasia, and megalencephaly). These disorders tend to be diagnosed and treated as separate clinical entities; a cross-disciplinary approach with a focus on shared underlying mechanisms is needed.

Severe ASDs, many of the most devastating epilepsies, intellectual disability syndromes, and brain malformations all manifest in early life (within the first 1-2 years) and have their origins in embryonic development. These disorders of brain development, which tend to co-occur, are all the focus of dedicated efforts to identify genetic factors. Genetic investigations into intellectual disability have largely followed the same path as for autism, with studies focused on identifying copy number variants, many of which overlap with those found in ASD.4 By contrast,