

Natural History of Spinocerebellar Ataxia Type 31: a 4-Year Prospective Study

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Abstract Spinocerebellar ataxia type 31 (SCA31) is known as a late-onset, relatively pure cerebellar form of ataxia, but a longitudinal prospective study on the natural history of SCA31 has not been done yet. In this prospective cohort study, we enrolled 44 patients (mean \pm standard deviation 73.6 ± 8.5 years) with genetically confirmed SCA31 from 10 ataxia referral centers in the Nagano area, Japan. Patients were evaluated every year for 4 years using the Scale for the Assessment and Rating of Ataxia (SARA) and the Barthel Index (BI). Of the 176 follow-up visits (91.5%), 161 were completed in this study. Five patients (11.4%) died during the follow-up period, and two patients (4.5%) were lost to follow-up. The annual progression of the SARA score was 0.8 ± 0.1 points/year and that of the BI was -2.3 ± 0.4 points/year (mean \pm standard error). Shorter disease duration at baseline was associated with faster progression of the SARA score. Our study indicated the averaged clinical course

of SCA31 as follows: the patients develop ataxic symptoms at 58.5 ± 10.3 years, become wheelchair bound at 79.4 ± 1.7 years, and died at 88.5 ± 0.7 years. Our prospective dataset provides important information for clinical trials of forthcoming disease-modifying therapies for cerebellar ataxia. It also represents a useful resource for SCA31 patients and their family members in genetic counseling sessions.

Keywords Spinocerebellar ataxia type 31 (SCA31) · Natural history · Scale for the assessment and rating of ataxia (SARA) · Barthel index

Introduction

Spinocerebellar ataxia type 31 (SCA31) (MIM 117210) accounts for 8–42% of autosomal dominant cerebellar ataxia

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(ADCA) families in Japan, with a considerable regional difference in frequency [1–7]. It is caused by a 2.5–3.8-kb insertion containing pentanucleotide repeats (TGGAA)_n, which is located in overlapping introns of the *BEAN* and *TK2* genes on chromosome 16q21–q22 [8, 9]. Recent progress in understanding the pathogenic mechanisms of ADCAs has raised hopes for the development of new disease-modifying therapies for cerebellar ataxia. Thus, knowledge about the natural history of ADCAs is important for well-designed clinical trials. To address these issues, some prospective cohort studies of patients with SCA1, SCA2, SCA3, or SCA6 have been conducted in Europe, the USA, Cuba, Taiwan, and Japan [10–15]. SCA31 may be a desirable ADCA subtype for clinical trials of forthcoming disease-modifying therapies for cerebellar ataxia because cerebellar Purkinje cells are preferentially affected in SCA31 [16–19]. Cross-sectional studies on the estimated clinical course of SCA31 have been reported [1–7]; however, prospective longitudinal studies on the rate of disease progression in SCA31 have not been performed. One possible reason for this is that SCA31 is almost exclusively seen in the Japanese population [20–22].

The main purpose of this study was to quantify the clinical progression rate of cerebellar ataxia and activities of daily living (ADLs) in SCA31 patients.

Methods

Organization and Patients of the Study

In this 4-year prospective cohort study, we enrolled 44 patients with genetically confirmed SCA31. We excluded the patients with any comorbid diseases that apparently prevented us from evaluating the severity of ataxia or ADLs. All patients were residents of Nagano prefecture, one of the most prevalent areas for SCA31 in Japan [6, 7], where the latest incidence of SCA31 is approximately 44% (103/235) of ADCA families. We calculated the size of Hae III fragment containing the insertion and substituted it for the TGGAA repeat length, as previously described [7, 8].

Patients were seen at a baseline visit (visit 1), followed by an annual evaluation (for a total of five visits) over a period of 4 years between 2011 and 2015. The present study was performed at 10 hospitals located in the Nagano area, Japan. A written informed consent form, which was approved by the institutional review board of all hospitals and by the Ethics Committee of the Shinshu University School of Medicine, was completed by all study participants.

Clinical Evaluation

Age at onset was determined on the basis of information provided by the patients themselves and their close relatives. We

used the Scale for the Assessment and Rating of Ataxia (SARA) and Barthel Index (BI) to evaluate the severity of ataxia [23] and ADLs of the patients [24], respectively. Each patient was followed by the same neurologist, who was experienced in neurology practice and trained for SARA.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics software (version 22; IBM, Armonk, NY, USA). To investigate whether the baseline characteristics of male patients differed from those of female patients, we used *t* tests for quantitative variables and χ^2 tests for categorical variables. Correlations between clinical scores and covariates were tested by the Pearson's correlation test. For analysis of disease progression, we applied a linear mixed model with random effects on the intercept and slope. The rate at which patients became wheelchair dependent and their survival were calculated by the Kaplan-Meier method. The test results were considered significant at the 0.05 level. To identify factors that affected the SARA score at baseline and delta SARA (Δ SARA), multiple regression analysis was used to validate the relationships between the SARA score and sex, age at onset, disease duration, and TGGAA repeat length of the expanded allele as independent variables. Independent factors that were significant in the univariate analysis were included in a multivariable model, including interactions with backward selection. Δ SARA was defined as the change of the SARA score between baseline and visit 5. The test results were considered significant at the 0.01 level for the multivariate analysis. Data are presented as means \pm standard error (SE), if not specified. To account for multiple testing, we used the Bonferroni correction and all *p* values were two sided.

Results

The study population consisted of 44 patients (male:female = 20:24) from 41 families with SCA31. The demographic data and clinical scores at baseline are summarized in Table 1. The age at baseline was 73.6 ± 8.5 years (mean \pm standard deviation [SD]). All patients presented with cerebellar ataxia (SARA score 4–31.5). By the Inventory of Non-Ataxia Signs (INAS) [25], increased ankle reflexes were seen in 12 (12/42, 28.6%), but only one patient (1/42, 2.4%) showed extensor plantar responses. Rigidity or involuntary movements were not observed in any patients, except for moderate facial dystonia in one patient. Dysphagia (16/42, 38.1%) and mild decrease of vibration sense (9/30, 30.0%) were relatively common in our cohort. Cognitive decline was noted in five patients (5/42, 11.9%). Seven patients (7/42, 16.7%) complained of mild double vision, but ophthalmoparesis or slowing of saccades was evident in only

Table 1 Demographic and clinical characteristics of the patient cohort

	All patients	Male	Female	<i>p</i> value
Number of patients	44	20	24	0.670
Age at baseline, years	73.6 ± 8.5 (55–89)	72.4 ± 8.8	74.6 ± 8.2	0.411
Age at disease onset, years	58.5 ± 10.3 (44–78)	56.4 ± 8.9	60.3 ± 9.9	0.217
Disease duration, years	15.1 ± 9.6 (1–31)	16.1 ± 9.1	14.3 ± 9.9	0.556
Total SARA score at baseline, points	16.5 ± 6.9 (4–31.5)	17.4 ± 7.5	15.8 ± 6.3	0.434
BI at baseline, points	82.5 ± 21.4 (30–100)	80.5 ± 20.9	84.2 ± 21.6	0.581
TGGAA repeat length of the expanded allele, kilo bases	3.3 ± 0.2 (2.7–3.8)	3.3 ± 0.3	3.3 ± 0.2	0.913

Where applicable, the values are given as the mean ± standard deviation (range). The *p* values were calculated with the use of *t* tests for quantitative variables and χ^2 tests for categorical variables

SARA Scale for the Assessment and Rating of Ataxia, BI Barthel Index, TGGAA thymine-guanine-guanine-adenine-adenine

two patients. Only a few patients showed mild autonomic dysfunction, urinary dysfunction in 2 (2/42, 4.8%) and constipation in 6 (6/44, 13.6%). The INAS count was 0.93 ± 1.18 (mean ± SD, $n = 42$, 75.5 ± 8.3 years at evaluation). Ten patients (10/43, 23.3%) showed hearing disturbance.

Figure e-1 shows the detailed data of patients followed each year and the reasons for dropout. All 44 patients were examined at a follow-up visit after 1 year (visit 2), but the number of patients examined at visit 3 decreased to 41 (93.2%), 39 (88.6%) at visit 4, and 37 (84.1%) at the final visit after 4 years (visit 5). Of the total 176 follow-up visits during the study period, 161 (91.5%) were completed. Five patients (11.4%) died during the follow-up period, three of pneumonia, one of congestive heart failure, and one of asphyxia (age at death 86.0 ± 3.2 years, SARA score and BI at their last visits 26.4 ± 5.9 and 42.0 ± 28.9 (mean ± SD), respectively). Additionally, two patients were lost to follow-up because of admission to a nursing home. Eleven of 44 patients were admitted to a hospital 15 times during the study period because of comorbid diseases such as infection, trauma, and cardiovascular diseases.

At baseline (visit 1), the mean SARA score was 16.5 ± 6.9 points and the BI was 82.5 ± 21.4 points (mean ± SD). Disease duration correlated well with both the SARA score and BI ($r = 0.699$, $p < 0.001$; $r = -0.620$, $p < 0.001$), and the age at baseline correlated well with both the SARA score and BI ($r = 0.629$, $p < 0.001$; $r = -0.477$, $p = 0.001$). In contrast to the previous report [7], the TGGAA repeat length of the expanded allele was not correlated with age at onset in this study. Among the 44 patients in this study, male patients tended to be younger and have a shorter disease duration than female patients; however, the difference was not statistically significant. In multiple regression analysis, 65.4% of the variance of the SARA at baseline score were explained. The SARA score was influenced by age at onset and disease duration. Unlike SCA6 in a Japanese cohort [15], the SARA score was not influenced by sex and TGGAA repeat length in SCA31 (Table 2).

There was a strong correlation ($r = -0.818$, $p < 0.001$) between the total SARA score and BI (Figure e-2). In most patients, the SARA score and BI worsened from year to year. The progression rates of both the SARA score and BI were best fitted with a linear model. The total SARA score

Fig. 1 Progression of SARA scores (a) and BI (b). The continuous black lines show the mean recorded values of all patients with SCA31. The bars represent the 95% CI. The dashed curves show the estimated progression

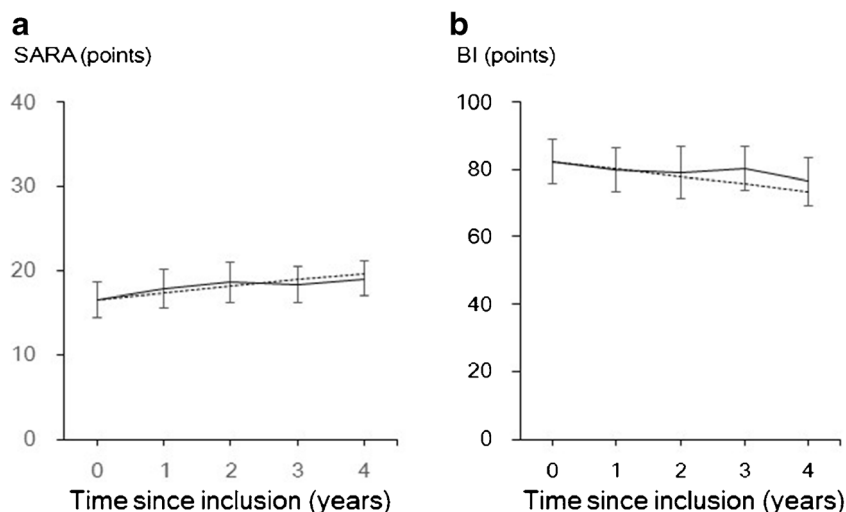


Table 2 Results of multivariate analysis for the SARA score at registration

R^2	p value	Effect	Estimate	SE	β	p value
0.654	<0.001					
		Intercept	-15.194	5.581	n/a	0.009
		Age at onset, years	0.376	0.100	0.521	0.001
		Disease duration, years	0.757	0.093	1.061	<0.001

SARA Scale for the Assessment and Rating of Ataxia, R^2 coefficient of determination, SE standard error, β standard coefficient, *n/a* not applicable

increased during the 4-year period by an average of 3.5 ± 0.5 points ($p < 0.001$ for the comparison with baseline) (Fig. 1a), and the BI decreased by an average of 10.3 ± 1.8 points ($p < 0.001$) (Fig. 1b). The annual progression of the SARA score and BI was 0.8 ± 0.1 and -2.3 ± 0.4 points/year, respectively.

Based on the progression of the SARA score, we calculated sample sizes needed for two-group interventional trials of 1-year duration. Estimated sample sizes per group to achieve 80 and 90% power with effect sizes ranging from 20 to 100% are shown in Figure e-3. In SCA31, a trial with 1112 patients (556 patients per group) would be able to detect a 50% reduction in progression of the SARA score. To identify factors that were independently associated with the Δ SARA score, we applied multiple regression analysis. In SCA31, shorter disease duration was associated with a larger Δ SARA score (-0.187 ± 0.65 per additional Δ SARA score; $p = 0.007$), but we did not identify any other factors for the decline in the SARA score (Table 3).

Among the subscores of SARA, the subscores for gait (baseline to 4-year visit 4.50 to 5.66 points, $p < 0.001$), stance (2.77 to 3.46 points, $p = 0.001$), finger chase (0.90 to 1.31, $p < 0.001$), fast alternating hand movements (1.53 to 2.21, $p < 0.001$), and heel-shin slide (2.35 to 2.71, $p = 0.031$) significantly declined over 4 years. The three other subscores, sitting (0.50 to 0.41), speech disturbance (2.74 to 2.92), and nose-finger test (1.25 to 1.27), showed no significant change over the same period. Table e-1 shows the results of subgroup analysis defined according to disease duration (<10, 10–19, ≥ 20 years). An annual decline of the SARA score was conspicuous in the subgroup with the shortest disease duration (<10 years). Among the subscores, changes to gait and stance constituted approximately 60% of the total changes in the subgroup with the shortest disease duration. However, this

change was not significant when compared with the subgroup with the longest disease duration.

Of 44 patients with SCA31, 13 (29.5%) were confined to a wheelchair at their initial visit (age; 78.7 ± 6.1 years, disease duration; 21.6 ± 11.6 years, mean \pm SD). Both their disease duration and age at baseline were different from those of the other 31 patients who were able to walk without a walking aid at their initial visit (age 71.5 ± 8.6 years, disease duration 12.4 ± 7.0 years, mean \pm SD). During this 4-year prospective study, 15 of the 31 ambulatory patients (48.4%) became wheelchair dependent. Figure 2a shows the Kaplan-Meier curve for the time at which patients became wheelchair dependent. The estimated mean of age of becoming wheelchair bound was 79.4 ± 1.7 years (95% confidence interval [CI] 76.0–82.8 years) and that of disease duration from onset to becoming wheelchair bound was 19.3 ± 1.5 years (95% CI 16.3–22.2 years).

Survival curves were calculated for overall survival according to the Kaplan-Meier method. Figure 2b shows the survival curve for the age at which patients died during the 4-year study period. The estimated means of disease duration and age at death were 37.9 ± 6.1 years (95% CI 26.0–50.0 years) and 88.5 ± 0.7 years (95% CI 87.0–89.9 years), respectively.

Discussion

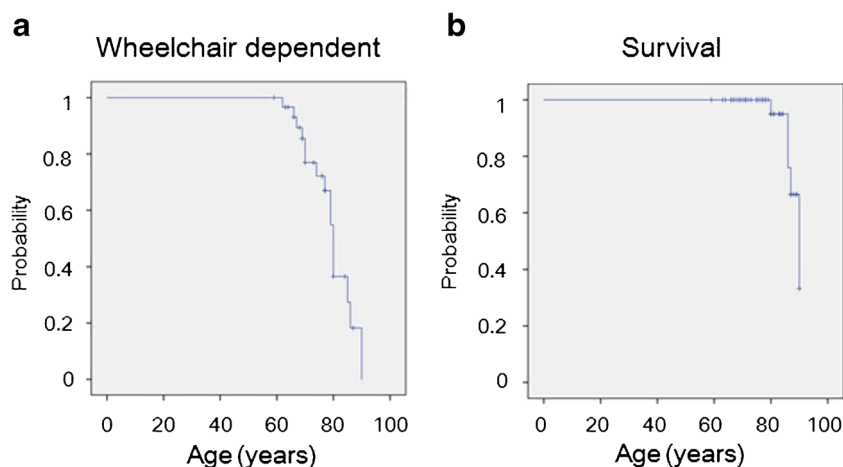
To our knowledge, this is the first report to assess a cohort of patients with SCA31 prospectively, providing quantitative evidence for the disease progression of SCA31 with a high follow-up rate. In this study, we completed a follow-up in 42 of 44 patients (95.5%), 37 until the last visit as initially planned and 5 until they died. Unfortunately, two patients

Table 3 Results of multivariate analysis for SARA progression

R^2	p value	Effect	Estimate	SE	β	p value
0.167	0.007					
		Intercept	6.216	1.108	n/a	<0.001
		Disease duration, years	-0.187	0.065	-0.436	0.007

SARA Scale for the Assessment and Rating of Ataxia, R^2 coefficient of determination, SE standard error, β standard coefficient, *n/a* not applicable

Fig. 2 Time for wheelchair dependency and survival plots indicating disease progression. **a** Kaplan-Meier graph showing time for wheelchair dependency based on age (**a**) and survival based on age (**b**) in patients with SCA31 ($n = 44$)



dropped out from the study because they were institutionalized to a nursing home during the study period.

At baseline, the clinical features of the patients in this study were consistent with those of previous cross-sectional studies, such as a late-onset and relatively pure cerebellar form of ataxia [1–7]. It was evident that the SARA score at baseline correlated well with both age at baseline and disease duration in SCA31 (Table 2). Further, there was a strong correlation between the SARA score and BI. The decline in the level of the ADLs of the patients started with a SARA score of more than 10 points (Figure e-2). It was clear that disturbance of the ADLs worsened in proportion to the severity of ataxia in the SCA31 patients. The present data showed that SCA31 patients became wheelchair dependent at approximately 80 years of age, indicating that SCA31 patients will need a wheelchair at approximately 20 years after disease onset. The mean life span of SCA31 patients was as long as that of the averaged one of the Japanese population, which was based on the recent statistical report in Japan [26].

In the present study, the SARA score declined by 0.8 points/year, and the annual decline of the SARA score was linear, despite heterogeneity among the patients. The decline of the SARA score in SCA6, the other predominant ADCA subtype of relatively pure cerebellar ataxias in Japan, was reported to range from 0.87 to 1.33 [10–15]. Therefore, we conclude that the disease progression of SCA31 is similar to or slightly slower than that of SCA6.

Our subgroup analysis showed that the annual progression rate of the SARA score decreased with disease duration and that disease progression reached a plateau at approximately 20 years after onset. Yasui et al. have pointed out that the same problem applied to SCA6 patients with severe ataxia (SARA score ≥ 25 points) [15]. One plausible reason for this is that the SARA score is an ordinal scale limited by ceiling. The SARA score may not be sufficiently sensitive for patients in the advanced stage of the disease. For the second plausible reason, no further active cerebellar degeneration might occur because almost all Purkinje cells have already gone.

The molecular defect in SCA31 is suggested to be an intronic insertion containing abnormally expanded TGGAA repeats in both *BEAN* and *TK2* [8, 9]. Therefore, as in SCA8 and myotonic dystrophy types 1 and 2 [27–29], a pathogenic RNA gain-of-function mechanism or repeat-associated non-ATG translation (RAN translation) mechanism may contribute to neurodegeneration in SCA31. Recently, the development of multiple strategies targeting the toxic RNA is in progress, and some clinical trials based on antisense oligonucleotides are ongoing [30]. Our data suggest that patients with a disease duration less than 10 years may be suitable candidates for clinical trials in SCA31, because an annual decline in the SARA subscores for gait and stance is clearly detected in patients at this stage. Even at this stage, however, the decline of the subscores for gait and stance was 0.61 (2.43/4) and 0.24 (0.96/4) points/year, respectively. Because of the subtle decline of the SARA score, we need a large number of patients to confirm the efficacy of interventional trials for SCA31 using SARA. Therefore, more sensitive and objective methods to assess the severity of gait and stance (for example, a triaxial accelerometer) is needed [31, 32].

For the study of the natural history of SCA31, we have to take some limitations into consideration. Firstly, the ages of the patients enrolled in this study were much older than those in other ADCA subtypes reported previously [6, 10–15]. Therefore, SCA31 patients are more likely to be complicated with other common diseases or age-dependent sarcopenia-frail syndrome. Actually, 25% of the patients needed to be hospitalized due to factors other than cerebellar ataxia in this study. Secondly, disease onset is quite insidious and sometimes difficult to recognize in SCA31, especially in late-onset patients. We were very careful with these factors when we enrolled the patients, but it is possible that they still influenced the SARA score and BI. Patient selection bias that SCA31 patients enrolled in this study were only from the limited area of Japan may not have a significant problem because almost all Japanese patients with SCA31 are known to be homogeneous genetically and phenotypically and share a similar lifestyle [1–8].

However, it is still unclear whether our longitudinal data can be applicable to SCA31 patients outside of Japan.

Conclusion

Our prospective cohort study confirmed a protracted clinical course and long life span in patients with SCA31. The average clinical course of SCA31 patients is as follows: they first notice ataxic symptoms at 58.5 ± 10.3 years of age (mean \pm SD), become wheelchair bound at 79.4 ± 1.7 years of age (mean \pm SE), and finally die at 88.5 ± 0.7 years of age (mean \pm SE). The present findings will help us not only conduct clinical trials for SCA31 patients but also inform SCA31 patients and their family members of disease prognosis.

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Compliance with Ethical Standards

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Conflict of Interest The authors declare that they have no conflict of interest.

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