Depression and clinical progression in spinocerebellar ataxias

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Depression and Clinical Progression in Spinocerebellar Ataxias

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Dr. Puls: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision

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Dr. Wilmot: acquisition of data

Dr. Gomez: acquisition of data

Dr. Schmahmann: acquisition of data

Dr. Paulson: acquisition of data

Dr. Shakkottai: acquisition of data

Dr. Ying: acquisition of data

Dr. Zesiewicz: acquisition of data

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Dr. Geschwind: acquisition of data

Dr. Xia: acquisition of data

Mr. Yu: analysis and interpretation

Ms. Lee: analysis and interpretation

Dr. Subramony: study concept and design, acquisition of data, study supervision

Dr. Ashizawa: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision

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Abstract

Background—Depression is a common comorbidity in spinocerebellar ataxias (SCAs) but its association with ataxia progression is not well understood.

Objectives—To study the prevalence and influence of depressive symptoms in SCAs.

Methods—We studied 300 participants with SCA 1, 2, 3 and 6 from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) and repeatedly measured depressive symptoms by the 9-item Patient Health Questionnaire (PHQ-9) along with other clinical features including ataxia, functional status, and quality of life every 6 months for 2 years. We employed regression models to study the effects of depressive symptoms on clinical progression indexed by Scale for Assessment and Rating of Ataxia (SARA), Unified Huntington’s Disease Rating Scale Part IV (UHDRS-IV) and EQ5D after adjusting for age, sex and pathological CAG repeats.

Results—Comorbid depression is common in SCAs (26%). Although the baseline prevalence of depression was similar among different SCA types, suicidal ideation was more frequently reported in SCA3 (65%). Depressive symptoms were associated with SARA scores but did not significantly progress over time within 2 years or deteriorate by increased numbers of pathological CAG repeats. The effects of depression on ataxia progression varied across different SCA types. Nevertheless, depression had consistently negative and significant impact on functional status and quality of life in all SCAs, even after accounting for ataxia progression.

Conclusions—Depressive symptoms are not simply the consequence of motor disability in SCAs. Comorbid depression per se contributes to different health outcomes and deserves more attention when caring patients with SCAs.

Keywords
depression; cerebellum; spinocerebellar ataxias; suicide; neurodegeneration

Introduction

Spinocerebellar ataxias (SCAs) are a group of autosomal-dominant cerebellar degenerative disorders with SCA 1, 2, 3, and 6 as the most common types [1,2]. In addition to adult-onset progressive cerebellar ataxia, other motor features such as pyramidal signs and eye
movement disorders are also often associated with SCAs [3]. Pathological CAG repeat expansions are the major genetic underpinning and the encoded polyglutamine aggregates are found in neurons of SCA brains [4]. The age of ataxia onset and the rate of disease progression are inversely associated with the number of pathological CAG repeats [1,2,5], indicating that the toxic effects of polyglutamine proteins and/or the repeat associated non-ATG translation products increase with longer repeat expansions [6]. The pathological CAG repeats, however, only explain 50-70% of the variability of the age of onset in SCAs [7-9], suggesting that factors other than CAG repeats may play a role in clinical progression in SCAs.

Depression is a common comorbidity in neurodegenerative disorders, such as Parkinson’s disease (PD) [10] and Huntington’s disease (HD) [11], and is thought to arise from neurodegeneration in the depression-related brain circuitry in these disorders. Depressive symptoms could even precede the motor impairment in PD and HD, arguing against that depression merely results from motor disability. Likewise, patients with SCA often have depressive symptoms [12]. Some studies report that depression is more frequently seen in SCA3 than other SCAs [13-15], but this finding is not consistently shown in others [12,16]. Depression has been proposed to be part of the neurodegeneration in SCAs [17-19], as cerebellum has dense connections with frontal lobes and multiple brainstem regions and cerebellar degeneration may lead to cognitive impairment and emotional disturbance, namely cerebellar cognitive affective syndrome [20]. Comorbid depression in SCA may indicate that the network involving cerebellum and limbic system is preferentially affected and thus the course of ataxia progression is likely different. The notion that non-motor symptoms may contribute to the motor deterioration has been extensively studied in HD [21] and PD [22], but not in SCAs yet.

The prevalence of depression in SCAs has been reported in a large cohort of SCA patients in EUROSCA, as defined by the 9-item Patient Health Questionnaire (PHQ-9) ≥10: 24.5% in SCA1, 20.3% in SCA2, 25.2% in SCA3, and 17.8% in SCA6 [12], which are similar to studies of fewer SCA patients in various populations[13-18,23]. However, few studies repeatedly measured depression together with ataxia severity in a longitudinal setting, and these studies were often hindered by small sample size [24,25]. Therefore, we used the longitudinal dataset from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) to investigate the prevalence of depression and how depressive symptoms evolve along with ataxia progression, functional status and quality of life in SCA 1, 2, 3, 6 during 2-year follow-ups.

**Methods**

**Study subjects**

The study participants were recruited by ataxia or movement disorders specialists during July 2009-May 2012 from 12 CRC-SCA centers [1]. These patients were referred to specialty clinics by patients themselves, community physicians, local support groups and the National Ataxia Foundation. The uniform study protocol was approved by the local institutional review boards and the informed consents were obtained from all participants. Our inclusion criteria were 1) the presence of ataxia, 2) definite genetic diagnosis of SCA1,
2, 3, or 6 either for the subject or another affected family member with ataxia, 3) willingness of participation, and 4) age of 6 and older. The exclusion criteria were 1) known recessive, X-linked and mitochondrial ataxias, 2) exclusion of SCA1, 2, 3, and 6 by previous genetic tests, 3) concomitant disorder(s) that affect ataxia measurements used in this study. Basic demographics were recorded and all participants were asked to provide blood samples for SCA genotyping. Study participants were followed every 6 months until 2 years from the baseline visit or the end of August 2012 when the study was closed. In each visit, a trained ataxia expert scored the severity of ataxia by the Scale for Assessment and Rating of Ataxia (SARA) and the Unified Huntington’s Disease Rating Scale part IV (UHDRS-IV), and assessed depressive symptoms by PHQ-9 during the interview [1,26,27].

**Genetic testing**

DNA samples from blood of 263 participants were obtained and CAG repeat expansions were determined in Dr. Stefan Pulst’s laboratory. For 37 patients whose blood samples were not available in the research lab, we used the repeat numbers from the commercial labs. In 19 patients, the information of CAG repeat expansion was not available (one SCA1, five SCA2, ten SCA3, three SCA6).

**Predictor variables**

We used PHQ-9 scores to reflect the severity of depressive symptoms. The PHQ-9 consists of nine questions to assess depressive mood over the past 2 weeks. Four levels were rated (not at all = 0; several days = 1; more than half the days = 2; nearly every day = 3) in each question, and higher scores (range, 0-27) reflect the severity of depression. PHQ-9 has been extensively studied as a tool to measure the severity of depression: none (0 - 4), mild (5 - 9), moderate (10 - 14), and severe (≥15) [28]. We defined clinically relevant depression as PHQ-9 ≥10, a commonly used and extensively validated cut-off point in previous studies [29]. Suicidal ideation was defined as scoring > 0 in item 9 of PHQ-9: thoughts that you would be better off dead or of hurting yourself in some ways in the past 2 weeks, which have been extensively studied in primary care patients [30,31].

**Outcome variables**

Although PHQ-9 was our major predictor for ataxia progression, we also examined factors that might affect PHQ-9, including ataxia severity, in a way to address the likely interaction or the causal effects in both directions. SARA was our outcome of interest, which measures 8 domains of motor performance in ataxia patients with a total score ranging from 0 to 40. Higher SARA scores reflected poor motor performance. There were 25 questions regarding functional performance in daily activities in UHDRS-IV. One point was given if the answer to the individual question was positive; the total score of UHDRS-IV ranged from 0 to 25, and higher scores indicated better functional status. EQ-5D was a standard instrument to measure health related quality of life. Two health outcome indicators were employed in the study: EQ-5D index score and EQ-VAS score. EQ-5D index was to score the best condition of the day (no problems = 1, moderate problems = 2, severe problems = 3) in 5 domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, with a total score ranging from 3 to 15. EQ-VAS score was estimated by asking participants his/her health
state of the day of the visit with a visual analogue scale from 0 = worst imaginable to 100 = best imaginable.

**Statistical analysis**

We compared the prevalence of baseline clinical relevant depression (PHQ9 ≥ 10) and suicidal ideation (PHQ-9 question 9 score > 0) in different SCA types using analysis of variance. We employed repeated measures linear regression (an exchangeable working within-subject correlation model via a generalized estimating equation (GEE)) to compute average rates of changes in depressive symptoms in each SCA group and to assess factors that might contribute to the progression of depressive symptoms. We used GEE models to study the associations between depression and the outcomes of interest including SARA, UHDRS-IV, and EQ5D after controlling for age, sex and pathological CAG repeat number. We further tested whether baseline depression was predictive of ataxia progression by putting baseline depression and its interaction with time rather than time-varying depressive symptoms into the model. SCA1, 2, 3 and 6 were treated as four independent cohorts and analyzed separately in regression models.

All statistical analyses and graphics were performed in the software R (version 2.11.1). All tests of statistical significance were conducted at the 2-tailed $\alpha$ level of 0.05.

**Results**

A total of 300 patients in CRC-SCA cohort were followed up with repeated measures of PHQ-9 scores and 19 SCA patients without PHQ-9 data were excluded (4 SCA1, 5 SCA2, 6 SCA3, and 4 SCA6). The baseline PHQ-9 scores were widely distributed (mean: 6.5; SD: 6.0; range: 0 - 26) and not significantly different in one SCA type than the other (ANOVA, $p = 0.16$). We found that the prevalence of clinically relevant depression (PHQ-9 ≥10) at baseline was common in all SCAs (SCA1: 24.5%, SCA2: 21.9%, SCA3: 30.9%, SCA6: 21.9%; ANOVA $p = 0.44$). Suicidal ideation was noticed in more than half of our study participants (52%) and was significantly more common in SCA3 (SCA1: 44.9%, SCA2: 45.3%, SCA3: 65.0%, SCA6: 39.1%; ANOVA $p < 0.01$) (Table 1).

Within the 2-year observation, PHQ-9 scores did not significantly change over time in all SCAs. We constructed GEE models to investigate factors that might affect depressive symptoms and found that time-varying SARA scores were associated with PHQ-9 scores in SCA1, 3, and 6, but not SCA2. In addition, longer disease duration was associated with higher PHQ-9 scores in SCA3 while increased number of CAG repeat was associated with lower PHQ-9 scores in SCA6. Age and sex did not play a significant role in PHQ-9 scores in these models (Supplemental table 1).

In the models which we tested whether depressive symptoms would affect ataxia progression, we found that increased time-varying PHQ-9 scores were associated with higher SARA scores in SCA1, 3, and 6; moreover, the effects of PHQ-9 scores on SARA scores remained significant even after accounting for age, sex, CAG repeats and time (Table 2). While replacing time-varying PHQ-9 scores with baseline PHQ-9 scores and its
interaction with time in the model, the role of depression in ataxia progression was less consistent (Supplemental table 2).

We further investigated the effects of PHQ-9 scores on functional performance and quality of life. After accounting for ataxia severity or SARA scores, higher levels of depression were still associated with poor functional status reflected by UHDRS-IV in the longitudinal models for SCA 1, 3 and 6. (Table 3) Similar effects of depression were also seen in the GEE models for quality of life measured by EQ-5D or EQ-VAS in all SCAs (Table 4 and Supplemental table 3). The contribution of depressive symptoms to functional state and quality of life was significant, independent of ataxia and consistent across different SCA types.

**Discussion**

In the present study, we found that depressive symptoms were common among patients with SCA. Depressive symptoms remained stable over time during the 2-year observation and appeared to be associated with higher SARA scores or greater severity of ataxia. UHDRS IV and ED-5Q were significantly influenced by depression after accounting for age, sex, CAG repeats and even SARA scores.

The prevalence of depression in our cohort (PHQ-9 ≥ 10: 26%) is largely similar to the European SCA patients [12] (PHQ-9 ≥ 10: 22%). It is noteworthy that the prevalence of suicidal ideation is significantly higher in SCA3 than other types, while the SARA score or ataxia severity of SCA3 is not much different than other types, suggesting that depression in SCA3 may partly result from the neurodegenerative process rather than merely a mood response to motor disability. Interestingly, our North American SCA cohorts have more than twice of the suicidal ideation than the European SCA patients (18.3% overall) [12], and much higher than the patients of primary care and mental health clinics (13%) [31]. Based on the same PHQ-9 criteria, our results suggest that SCA patients are indeed a high risk population for suicidal ideation, although culturally sensitive and geographically dependent factors should also be taken into account. Our findings highlight the importance of early recognition of depression when caring for SCA patients.

The association between ataxia severity and depressive symptoms suggests that patient perception of disability contributes to depression in SCAs. However, several lines of evidence showed that depression might not be solely attributed to motor disability. First, in the natural history study of SCAs, ataxic symptoms deteriorated at different rates in different SCAs: the fastest in SCA1, followed by SCA3, SCA2, and SCA6 [1]. However, the prevalence of depression did not follow the same rank order of progression (SCA3 > SCA1 > SCA2 > SCA6), suggesting other factors must be also considered. Second, unlike ataxia severity, depressive symptoms do not seem to change over time or change along with the motor disability, at least within the 2-year observation. Even at baseline, where SARA scores were highest in SCA2 than other types, SCA2 patients did not have higher prevalence of depression. Third, when treating depression as the predictor for ataxia progression in the model, the link between depressive symptoms and SARA scores remained significant after accounting for age, sex, pathological CAG repeat and time, suggesting that depression per se
might also contribute to ataxia progression or at least go along with ataxic symptoms under the same overarching pathomechanism.

Our findings are in line with the cerebellar cognitive affective syndrome in which depression reflects the dysfunction of cerebellar connection to limbic system or a widespread disease progression [32]. In fact, the pathological studies of SCAs have shown that several brainstem areas and limbic systems, which are implicated in depression, have neuronal polyglutamine inclusions, including the raphe nuclei and locus ceruleus [4]. The clinically relevant depression implies the pathological involvement of these brain networks, and thus developed along with ataxia progression. The SARA score evolves as the neurodegenerative process progressively affects the motor cerebellum located principally in the anterior lobe (mostly lobules III - V), parts of lobule VI, and lobule VIII. The depression may be deepening along with the SARA score because of progressive neurodegenerative involvement affecting the cognitive - limbic cerebellum in the vermis and lateral aspects of the cerebellar posterior lobe, namely, lobules VI and VII (including Crus I, Crus II and lobule VIIb) [32]. Interestingly, the pathology of SCA6 mostly was restricted to the cerebellum [4], and we also observed a high prevalence of depression in SCA6, supporting the notion that cerebellar network is involved in depressive symptoms in SCAs. Although depression is likely originated from the underlying neuropathological changes of SCAs, its severity does not go along with motor deterioration, suggesting that depression is an intrinsic feature of neurodegeneration rather than a symptom reflecting pathological progression [33].

The negative impact of depression on functional status and quality of life was found independent of ataxia severity and significant in SCA1, 3 and 6. More importantly, when we take a closer look at the magnitude of the impact (per unit change) based on their β coefficients, the impact of depression is about 1/3 of ataxia severity on UHDRS-IV and almost equivalent to ataxia severity on EQ-5D. These findings underscore the importance of depression in SCA that non-motor features may contribute to the prognosis and life quality of SCA no less than motor disability. Selective serotonin reuptake inhibitors (SSRIs) have been a mainstay of therapy for depression, and lately, a SSRI, citalopram, has been shown to reduce the neurotoxicity in SCA3 animal models [34] and exert neuroprotective effects in stroke patients [35]. Future clinical trials are needed to test SSRIs in SCA patients.

The main strength of current study is its longitudinal design with repeated measures of SARA, UHDRS-IV, PHQ-9, and EQ-5D every 6 months in one of the largest cohorts of SCA patients, which allows us to address the rates of change in different aspects of neurodegeneration in SCAs. To extend the observation of the same cohort beyond 2 years is warranted if we aim to evaluate other non-motor features of SCA with respect to natural history or therapeutic effects.

There are some limitations in our study. First, we employed only PHQ-9 to assess the level of depression during interview. Although this tool has been validated in previous studies [28,31], a formal psychiatric interview remains a critical approach to evaluate the emotional state of patients comprehensively. Besides, cognitive function and other neuropsychiatric symptoms were not formally examined or systematically collected in this cohort, which...
limited our view regarding the effects of non-motor features on ataxia progression. Second, we did not have information on the onset of depression as these patients were recruited cross-sectionally with different duration of ataxia and non-motor features at baseline. Longer disease duration before enrollment was associated with depression only in SCA3 but not in other types, thus depression may not necessarily be the consequence of longstanding suffering and can be treated as an independent feature. Third, we do not have an age and sex-matched control group to compare the degree of depression with patients who may have other neurological diseases but with comparable levels of motor disability. To demonstrate that depression comes from the dysfunction of the connection between cerebellum and limb system, a case-control design is much preferred. Fourth, we recorded the suicidal ideation by the item 9 of PHQ-9 ≥ 0 and the clinically relevant depression using the sum of PHQ-9 scores ≥ 10, and these cut-off have been applied to not only SCA patients [12] but also general population [28,31]. We found that a significant portion of SCA patients did not reach the clinically relevant depression but still had suicidal ideation. The item 9 of PHQ-9 has been well studied to predict subsequent suicidal attempt and suicide death in the general population [31], highlighting the need that clinicians should pay close attention to the suicidal ideation in SCA patients. Fifth, we did not know whether SCA patients who lived with their affected family members would be more depressed, which would be an important factor to take into account in the future studies.

In conclusion, depression is a common comorbidity in SCA. In the relation with ataxia, depression can be both the emotional response to suffering and part of neurodegeneration in SCAs. After accounting for ataxia severity, depressive symptoms still have significant and negative impact on different aspects of health outcome, highlighting the need of paying more attention to depression when caring patients with SCAs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References


**Highlight**

1. Depression is common in SCAs and depressive symptoms do not progress over 2 years.
2. Suicidal ideation is more prevalent in SCA3.
3. The effects of depression on ataxia progression vary across different SCA types.
4. Depression has consistently negative impact on functional status and quality of life in all SCAs, after accounting for ataxia progression.
Table 1
Baseline features of 300 participants in the CRC-SCA with PHQ-9 data available.

<table>
<thead>
<tr>
<th>Demographic feature</th>
<th>SCA 1</th>
<th>SCA 2</th>
<th>SCA 3</th>
<th>SCA 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n</td>
<td>49</td>
<td>64</td>
<td>123</td>
<td>64</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>50.2 (12.8)</td>
<td>51.3 (13.4)</td>
<td>51.1 (12.4)</td>
<td>65.0 (10.5)</td>
</tr>
<tr>
<td>Sex, M : F</td>
<td>23 : 26</td>
<td>26 : 38</td>
<td>59 : 64</td>
<td>29 : 35</td>
</tr>
<tr>
<td>White race, %</td>
<td>89.8</td>
<td>75.0</td>
<td>52.8</td>
<td>90.6</td>
</tr>
<tr>
<td>Mean age of onset (SD)</td>
<td>40.5 (11.9)</td>
<td>36.4 (11.8)</td>
<td>38.8 (11.9)</td>
<td>51.8 (10.5)</td>
</tr>
<tr>
<td>N=63</td>
<td>N=121</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean disease duration (SD)</td>
<td>8.5 (6.7)</td>
<td>13.9 (8.5)</td>
<td>11.4 (7.7)</td>
<td>11.6 (10.6)</td>
</tr>
<tr>
<td>N=63</td>
<td>N=122</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median repeats (range)</td>
<td>46 (37-55)</td>
<td>39 (23-49)</td>
<td>71 (60-79)</td>
<td>22 (22-27)</td>
</tr>
<tr>
<td>N=48</td>
<td>N=60</td>
<td>N=113</td>
<td>N=61</td>
<td></td>
</tr>
<tr>
<td>SARA score, mean (SD)</td>
<td>14.2 (8.5)</td>
<td>16.9 (7.4)</td>
<td>15.0 (8.8)</td>
<td>14.3 (7.5)</td>
</tr>
<tr>
<td>PHQ-9, mean (SD)</td>
<td>6.1 (6.7)</td>
<td>5.3 (5.4)</td>
<td>7.3 (5.8)</td>
<td>6.5 (6.0)</td>
</tr>
<tr>
<td>Depression, n</td>
<td>12 (24.5%)</td>
<td>14 (21.9%)</td>
<td>38 (30.9%)</td>
<td>14 (21.9%)</td>
</tr>
<tr>
<td>Suicidal ideation, n</td>
<td>22 (44.9%)</td>
<td>29 (45.3%)</td>
<td>80 (65.0%)</td>
<td>25 (39.1%)</td>
</tr>
<tr>
<td>Use of SSRI, n</td>
<td>15 (30.6%)</td>
<td>15 (23.4%)</td>
<td>27 (22.0%)</td>
<td>22 (34.4%)</td>
</tr>
</tbody>
</table>

Abbreviations: CRC-SCA = the Clinical Research Consortium for Spinocerebellar Ataxias; PHQ-9 = Patient Health Questionnaire; SCA = Spinocerebellar ataxia; SARA = Scale for assessment and rating of ataxia. SSRI: selective serotonin reuptake inhibitor. Depression is defined as PHQ-9 score ≥ 10. Suicidal ideation is defined as scoring 1-3 in question 9 of PHQ: thoughts that you would be better off dead or of hurting yourself in some ways in the past 2 weeks.
Table 2

Longitudinal PHQ-9 scores and SARA scores in a GEE model.

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficient in GEE models of SARA scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCA 1</td>
</tr>
<tr>
<td></td>
<td>N=49</td>
</tr>
<tr>
<td>Age</td>
<td>0.25</td>
</tr>
<tr>
<td>Sex</td>
<td>3.41</td>
</tr>
<tr>
<td>CAG repeat</td>
<td>0.53</td>
</tr>
<tr>
<td>Time</td>
<td>0.14*</td>
</tr>
<tr>
<td>Time-varying</td>
<td>0.15*</td>
</tr>
<tr>
<td>PHQ-9 score</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05. Abbreviations: PHQ-9 = Patient Health Questionnaire; GEE = Generalized Estimating Equation; SCA = Spinocerebellar ataxia; SARA = Scale for assessment and rating of ataxia.

Entries are regression coefficients in the GEE models with the time-varying SARA scores as the outcome of interest and age (year), sex (M/F), pathologic CAG repeat number (N), time (month), and time-varying PHQ-9 scores as predictors. The regression coefficients can be interpreted as the change of SARA score per unit change of the predictor variables.
Table 3

Time-varying PHQ-9 scores and UHDRS-IV scores in a GEE model.

<table>
<thead>
<tr>
<th>Regression coefficient in GEE models of UHDRS IV scores</th>
<th>SCA 1 N=49</th>
<th>SCA 2 N=64</th>
<th>SCA 3 N=118</th>
<th>SCA 6 N=64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.02</td>
<td>0.01</td>
<td>−0.15 *</td>
<td>−0.15 *</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.33</td>
<td>0.001</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>CAG repeat</td>
<td>−0.07</td>
<td>−0.02</td>
<td>−0.55 *</td>
<td>−0.86</td>
</tr>
<tr>
<td>Time</td>
<td>0.03</td>
<td>−0.003</td>
<td>−0.08 *</td>
<td>−0.03</td>
</tr>
<tr>
<td>SARA score</td>
<td>−0.56 *</td>
<td>−0.58 *</td>
<td>−0.46 *</td>
<td>−0.38 *</td>
</tr>
<tr>
<td>PHQ-9 score</td>
<td>−0.17 *</td>
<td>−0.11</td>
<td>−0.15 *</td>
<td>−0.10 *</td>
</tr>
</tbody>
</table>

*p < 0.05. Abbreviations: PHQ-9 = Patient Health Questionnaire; UHDRS-IV = Unified Huntington’s Disease Rating Scale part IV; GEE = Generalized Estimating Equation; SCA = Spinocerebellar ataxia.

Entries are regression coefficients in the GEE models with the time-varying UHDRS-IV scores as the outcome of interest and higher scores indicate better function. Age (year), sex (M/F), pathologic CAG repeat number (N), time (month), time-varying SARA score and time-varying PHQ-9 score as predictors. The regression coefficients can be interpreted as the change of UHDRS-IV score per unit change of the predictor variables.
Table 4
Time-varying PHQ-9 scores and EQ-5D scores in a GEE model.

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficient in GEE models of EQ-5D scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCA 1 N=49</td>
</tr>
<tr>
<td></td>
<td>SCA 2 N=64</td>
</tr>
<tr>
<td></td>
<td>SCA 3 N=118</td>
</tr>
<tr>
<td></td>
<td>SCA 6 N=64</td>
</tr>
<tr>
<td>Age</td>
<td>2.6 × 10^{-3}</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.57*</td>
</tr>
<tr>
<td>Pathologic CAG repeat</td>
<td>0.02</td>
</tr>
<tr>
<td>Time</td>
<td>-0.002</td>
</tr>
<tr>
<td>SARA score</td>
<td>0.12*</td>
</tr>
<tr>
<td>PHQ-9 score</td>
<td>0.12*</td>
</tr>
</tbody>
</table>

Entries are regression coefficients in the GEE models with the time-varying EQ-5D scores as the outcome of interest and higher scores indicate better function. Age (year), sex (M/F), pathologic CAG repeat number (N), time (month), time-varying SARA score and time-varying PHQ-9 score as predictors. Higher EQ-5D scores indicate poor quality of life. The regression coefficients can be interpreted as the change of EQ-5D score per unit change of the predictor variables.

* $p < 0.05$. Abbreviations: EQ-5D = quality of life measurement from 5 domains; PHQ-9 = Patient Health Questionnaire; GEE = Generalized Estimating Equation; SCA = Spinocerebellar ataxia.