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Vascular Risk Factors and Clinical Progression in Spinocerebellar Ataxias

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Abstract

Background: The contributions of vascular risk factors to spinocerebellar ataxia (SCA) are not known.

Methods: We studied 319 participants with SCA 1, 2, 3, and 6 and repeatedly measured clinical severity using the Scale for Assessment and Rating of Ataxia (SARA) for 2 years. Vascular risk factors were summarized by CHA²DS²-VASc scores as the vascular risk factor index. We employed regression models to study the effects of vascular risk factors on ataxia onset and progression after adjusting for age, sex, and pathological CAG repeats. Our secondary analyses took hyperlipidemia into account.

Results: Nearly 60% of SCA participants were at low vascular risks with CHA²DS²-VASc = 0, and 31% scored 2 or greater. Higher CHA²DS²-VASc scores were not associated with either earlier onset or faster progression of ataxia. These findings were not altered after accounting for hyperlipidemia.

Discussion: Vascular risks are not common in SCAs and are not associated with earlier onset or faster ataxia progression.

Keywords: Hypertension, hyperlipidemia, vascular, spinocerebellar ataxias, neurodegeneration

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Introduction

CAG repeat disorders are a group of neurodegenerative diseases, including Huntington’s disease (HD), dentatorubral-pallidoluysian atrophy, and spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, and 17, and others. These diseases are inherited in an autosomal dominant fashion and neuropathological findings usually reveal neuronal inclusions of polyglutamine aggregates.¹ The age of onset and disease progression in ataxia are inversely associated with the number of pathological CAG repeats.² ³ Polyglutamine repeat expansions cause defective protein quality control and mitochondrial dysfunction leading to neuronal death.⁴ The pathological CAG repeats, however, explain only 50–70% of the variability of the age of disease onset in CAG repeat-related SCAs, suggesting the existence of disease modifiers other than CAG repeats.⁵ ⁸

Cerebrovascular disease, atherosclerosis, hypertension, diabetes mellitus, and hyperlipidemia, are associated with vascular dementia and Alzheimer’s disease (AD).⁹ Vascular pathology is often seen in elderly patients with various types of dementia. The concept of neurovascular units has been proposed to explain the vascular contributions to neurodegeneration; blood–brain barrier breakdown,
Vascular Risk Factors in Spinocerebellar Ataxias

Figure 1A. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1B. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1C. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1D. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1E. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1F. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1G. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1H. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1I. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1J. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1K. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1L. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1M. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1N. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1O. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1P. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1Q. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1R. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1S. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1T. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.

Figure 1U. Hypopituitarism caused by hyperpituitarism in a 2-year-old boy. A: Anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. B: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period. C: Comparison of anterior and posterior pituitary hormone levels at baseline and at the end of the 2-year observation period.
Coefficients of the interaction terms reflected the direction and magnitude of how vascular risk factors modified the disease course in SCAs. In a different linear regression model, we treated age of disease onset as the outcome and assessed whether CHA2DS2-VASc scores were associated with earlier onset of ataxia.

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

## Results

A total of 319 patients in the CRC-SCA cohort were followed up with repeated measures of SARA scores, and the mean CHA2DS2-VASc score was 0.9. The baseline demographics and functional states of SCA1, 2, 3, 6 were tabulated (Table 1). We found that nearly 60% of all SCA participants had low cerebrovascular risk factors with CHA2DS2-VASc $\leq 0$, and 31% scored 2 or greater (range 0–9; 1, 8.8%; 2, 19.4%; 3, 8.2%; 4, 2.5%; 5, 0.3%; 6, 0.3%). The SCA6 group was older at enrollment and with higher baseline vascular risk factors than SCA1, 2, and 3. The mean SARA score (0–40) at baseline was 15.1, and the SARA scores captured the progression of ataxia at a rate of 0.92 point/year.

Higher baseline CHA2DS2-VASc scores were associated with higher levels of ataxia severity in SCA3 and 6 in univariate models but the associations disappeared after adjusting for age. CHA2DS2-VASc scores did not modify the rates of progression of SARA scores in all SCA participants either. The progression of SARA scores was mostly determined by age, time, and CAG repeat number. These findings were not altered after accounting for hyperlipidemia (Table 2). In addition, disease onset was significantly associated with CAG repeat numbers and enrollment age but not associated with CHA2DS2-VASc scores (Table 2).

## Discussion

In the present study, vascular risk factors indexed by CHA2DS2-VASc scores were not associated with age at disease onset or clinical progression in patients with SCAs. We did not find evidence in the

### Table 1. Clinical Features of 319 Participants in the Clinical Research Consortium-Spinocerebellar Ataxia at Enrollment

<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>53</td>
<td>69</td>
<td>129</td>
<td>68</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>50.3 (13.0)</td>
<td>50.9 (13.5)</td>
<td>51.4 (12.3)</td>
<td>65.5 (10.8)</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>24:29</td>
<td>29:40</td>
<td>62:67</td>
<td>30:38</td>
</tr>
<tr>
<td>White race, %</td>
<td>90.6</td>
<td>73.9</td>
<td>54.2</td>
<td>91.2</td>
</tr>
<tr>
<td>Mean age of onset (SD)</td>
<td>40.2 (11.7)</td>
<td>36.4 (11.9)</td>
<td>38.9 (11.9)</td>
<td>52.3 (10.4)</td>
</tr>
<tr>
<td>Mean disease duration (SD)</td>
<td>8.8 (6.9)</td>
<td>13.6 (8.3)</td>
<td>11.5 (7.8)</td>
<td>11.7 (10.5)</td>
</tr>
<tr>
<td>Median repeats (range)</td>
<td>46 (37–59)</td>
<td>39 (23–49)</td>
<td>71 (60–79)</td>
<td>22 (22–27)</td>
</tr>
<tr>
<td>Functional state</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARA score (SD)</td>
<td>14.4 (8.2)</td>
<td>17.1 (7.4)</td>
<td>15.1 (8.9)</td>
<td>14.1 (7.4)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc scores (SD)</td>
<td>0.4 (0.9)</td>
<td>0.7 (1.1)</td>
<td>0.7 (1.1)</td>
<td>1.6 (1.5)</td>
</tr>
<tr>
<td>[0: 77%]</td>
<td>[0: 67%]</td>
<td>[0: 63%]</td>
<td>[0: 37%]</td>
<td></td>
</tr>
<tr>
<td>Modified CHA2DS2-VASc scores (SD)</td>
<td>0.5 (1.1)</td>
<td>0.8 (1.2)</td>
<td>0.8 (1.1)</td>
<td>1.8 (1.6)</td>
</tr>
<tr>
<td>[0: 73%]</td>
<td>[0: 64%]</td>
<td>[0: 61%]</td>
<td>[0: 34%]</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHA2DS2-VASc, Clinical Predictive Score Based on Congestive Heart Failure, Hypertension, Age $\geq$75, Diabetes, Prior Stroke, Vascular Disease, Age 65–74, Sex Category; SARA, Scale for Assessment and Rating of Ataxia; SCA, Spinocerebellar Ataxia; SD, Standard Deviation.
Table 2. Effects of Vascular Risk Factors on Ataxia Progression and Onset in Regression Models

<table>
<thead>
<tr>
<th>CHA2DS2-VASc model</th>
<th>Regression Coefficient in GEE Models (outcome: SARA score)</th>
<th>Regression Coefficient in Linear Regression Models (outcome: age at onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCA 1</td>
<td>SCA 2</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.22</td>
<td>0.27*</td>
</tr>
<tr>
<td>Female</td>
<td>4.65*</td>
<td>−1.89</td>
</tr>
<tr>
<td>CAG repeat</td>
<td>0.36</td>
<td>1.05*</td>
</tr>
<tr>
<td>CHA2DS2-VASc scores</td>
<td>−2.06</td>
<td>0.28</td>
</tr>
<tr>
<td>Time, minutes</td>
<td>0.14*</td>
<td>0.10*</td>
</tr>
<tr>
<td>CHA2DS2-VASc × time</td>
<td>−0.04</td>
<td>−0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified CHA2DS2-VASc model</th>
<th>Regression Coefficient in GEE Models (outcome: SARA score)</th>
<th>Regression Coefficient in Linear Regression Models (outcome: age at onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCA 1</td>
<td>SCA 2</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.23</td>
<td>0.27*</td>
</tr>
<tr>
<td>Female</td>
<td>4.63</td>
<td>−1.90</td>
</tr>
<tr>
<td>CAG repeat</td>
<td>0.41</td>
<td>1.04*</td>
</tr>
<tr>
<td>Modified CHA2DS2-VASc</td>
<td>−1.38</td>
<td>0.28</td>
</tr>
<tr>
<td>Time, minutes</td>
<td>0.14*</td>
<td>0.11*</td>
</tr>
<tr>
<td>Modified CHA2DS2-VASc × time</td>
<td>−0.02</td>
<td>−0.04</td>
</tr>
</tbody>
</table>

Abbreviations: CHA2DS2-VASc, Clinical Predictive Score Based on Congestive Heart Failure, Hypertension, Age ≥75, Diabetes, Prior Stroke, Vascular Disease, Age 65–74, Sex Category; GEE, Generalized Estimating Equation; SARA, Scale for Assessment and Rating of Ataxia; SCA, Spinocerebellar Ataxia.

*p < 0.05.
CRC-SCA cohort to support the notion that vascular risk factors would contribute to neurodegeneration in SCAs.

Our study has several strengths. First, this is one of the largest SCA cohorts diagnosed and evaluated by ataxia experts, allowing us to examine common vascular risks in rare diseases both at the population level and with high clinical certainty. Second, the role of vascular risk factors in neurodegeneration has not been well studied in monogenic CAG repeat-related ataxias before. Our findings filled the gap for research focusing on neurovascular integrity and neurodegeneration.

The study limitations mainly came from measurement error. First, CHA2DS2-VASc scores may not reflect cerebrovascular conditions well. The score is originally designed for patients with atrial fibrillation to predict their future stroke risks. Based on the available information, we could not develop Framingham Cardiovascular Risk Scores or directly measure the load of cerebrovascular lesions by brain imaging. Vascular risk data should be systematically collected to better study their roles in neurodegenerative diseases. Second, most of these patients are relatively young, except for SCA6 subjects, and do not have vascular comorbidity, which limited our power to detect the effect of vascular risk factors. Third, although SARA scores measure clinical severity of ataxia well, we do not have any pathological evidence or biomarkers to track progression in SCAs. Future studies may search for more evidence of vascular pathology in the cerebellum for patients with SCAs to determine the likelihood of vascular contributions.

In conclusion, disease onset and progression in SCA 1, 2, 3, and 6 are mainly determined by CAG repeats and are likely independent of common vascular risk factors. Vascular contributions to neurodegeneration found within the context of cerebral ischemia or amyloid deposition in dementia may not apply to SCAs.

References