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Raymond Y. Yo, Tzu Chi University
Karla P. Figueroa, University of Utah
Stefan M. Pulst, University of Utah
Chi-Ying Lin, Columbia University
Susan Perlman, University of California Los Angeles
George Wilmot, Emory University
Christopher M. Gomez, University of Chicago
Jeremy Schmahmann, Harvard University
Henry Paulson, University of Michigan, Ann Arbor
Vikram G. Shakkottai, University of Michigan, Ann Arbor

Only first 10 authors above; see publication for full author list.

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Brief Reports

**Vascular Risk Factors and Clinical Progression in Spinocerebellar Ataxias**

Raymond Y. Lo 1, Karla P. Figueroa 2, Stefan M. Pulst 2, Chi-Ying Lin 3, Susan Perlman 4, George Wilmot 5, Christopher M. Gomez 6, Jeremy Schmahmann 7, Henry Paulson 8, Vikram G. Shakkottai 8, Sarah H. Ying 9, Theresa Zesiewicz 10, Khalf Bushara 11, Michael Geschwind 12, Guangbin Xia 13, S. H. Subramony 13, Tetsuo Ashizawa 13 & Sheng-Han Kuo 3*

1 Department of Neurology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan, 2 Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA, 3 Department of Neurology, University of California, Los Angeles, CA, USA, 4 Department of Neurology, Emory University, Atlanta, GA, USA, 5 Department of Neurology, University of Utah, Salt Lake City, UT, USA, 6 Department of Neurology, University of California, Los Angeles, CA, USA, 7 Department of Neurology, Emory University, Atlanta, GA, USA, 8 Department of Neurology, University of Chicago, Chicago, IL, USA, 9 Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, 10 Department of Neurology, University of Michigan, Ann Arbor, MI, USA, 11 Department of Neurology, Johns Hopkins University, Baltimore, MD, USA, 12 Department of Neurology, University of South Florida, Tampa, FL, USA, 13 Department of Neurology, University of Minnesota, Minneapolis, MN, USA, 13 Department of Neurology and McKnight Brain Institute, University of Florida, Gainesville, FL, USA

**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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*To whom correspondence should be addressed. E-mail: sk3295@columbia.edu

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**Financial Disclosures:** None.

**Conflict of Interest:** The authors report no conflicts of interest.

**Introduction**

CAG repeat disorders are a group of neurodegenerative diseases, including Huntington’s disease (HD), dentatorubral-pallidolysian 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 have also been studied in Parkinson’s disease (PD). Hypertension and diabetes do not seem to directly contribute to the risk of PD, whereas increased blood cholesterol levels are associated with a higher risk of PD. Interestingly, statin use is associated with a lower risk of PD and discontinuation of statin use has an opposite effect. Vascular risk factors and cerebral white matter hyperintensity are associated with mild cognitive impairment in PD. In amyotrophic lateral sclerosis, hyperlipidemia is a good prognostic factor. Microvascular abnormality has been identified in post-mortem HD brains and the presence of additional vascular insults could further influence the disease progression. Despite the extensive interest in vascular risk factors in neurodegenerative diseases, the concept has not yet been successfully applied to SCAs.

Anatomically, the cerebellum and brainstem are two heavily involved regions in SCA1, 2, and 3 whereas the pathology of SCA6 is relatively restricted to the cerebellum. These brain regions are prone to vascular insults as ataxia-hemiparesis and dysarthria-clumsy hand are classical symptoms for lacunar infarcts. Interestingly, increased white matter vascular burden in the cerebellum has been observed in another cerebellar disorder, essential tremor. These brain regions are involved regions in SCA1, 2, and 3 whereas the pathology of SCA6 is relatively restricted to the cerebellum. The neurovascular change may have well elucidated the disordered amyloid metabolism in AD and the mixture of vascular and AD pathologies commonly seen in dementia. Hypoperfusion, and endothelial dysfunction likely lead to neuronal dysfunction. The neurovascular change may have well elucidated the disordered amyloid metabolism in AD and the mixture of vascular and AD pathologies commonly seen in dementia.

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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 CHA 2DS2-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 \( \alpha \)-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 CHA 2DS2-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 CHA 2DS2-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 CHA 2DS2-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. CHA 2DS2-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 CHA 2DS2-VASc scores (Table 2).

**Discussion**

In the present study, vascular risk factors indexed by CHA 2DS2-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 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>
</tr>
</thead>
<tbody>
<tr>
<td>Regression Coefficient in GEE Models (outcome: SARA score)</td>
</tr>
<tr>
<td>Regression Coefficient in Linear Regression Models (outcome: age at onset)</td>
</tr>
<tr>
<td>SCA 1</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>CAG repeat</td>
</tr>
<tr>
<td>Modified CHA2DS2-VASc</td>
</tr>
<tr>
<td>Time, minutes</td>
</tr>
<tr>
<td>Modified CHA2DS2-VASc × time</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