

## Brief Reports

## 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 CHA<sub>2</sub>DS<sub>2</sub>-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 CHA<sub>2</sub>DS<sub>2</sub>-VASc=0, and 31% scored 2 or greater. Higher CHA<sub>2</sub>DS<sub>2</sub>-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-pallidolusian 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.<sup>1</sup> The age of onset and disease progression in ataxia are inversely associated with the number of pathological CAG repeats.<sup>2,3</sup> Polyglutamine repeat expansions cause defective protein quality control and mitochondrial dysfunction

leading to neuronal death.<sup>4</sup> 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.<sup>5–8</sup>

Cerebrovascular disease, atherosclerosis, hypertension, diabetes mellitus, and hyperlipidemia, are associated with vascular dementia and Alzheimer's disease (AD).<sup>9</sup> 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,

hypoperfusion, and endothelial dysfunction likely lead to neuronal dysfunction.<sup>10</sup> 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.

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.<sup>11</sup> Interestingly, statin use is associated with a lower risk of PD<sup>12</sup> and discontinuation of statin use has an opposite effect.<sup>13</sup> Vascular risk factors and cerebral white matter hyperintensity are associated with mild cognitive impairment in PD.<sup>14</sup> In amyotrophic lateral sclerosis, hyperlipidemia is a good prognostic factor.<sup>15</sup> Microvascular abnormality has been identified in post-mortem HD brains<sup>16</sup> 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.<sup>17</sup> 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.<sup>18</sup> These findings emphasize the potential role of vascular risk factors in cerebellar ataxia disorders.

We herein tested the hypothesis of neurovascular concept outside the dementia context by studying the role of vascular risk factors in disease onset and progression in SCA types 1, 2, 3, and 6 from the Clinical Research Consortium-Spinocerebellar Ataxia (CRC-SCA).

## Methods

### Study subjects

Three hundred and nineteen study participants were recruited by ataxia or movement disorders specialists during July 2009 to May 2012 from 12 CRC-SCA centers. The uniform study protocol was approved by the local institutional review boards and 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 for another affected family member with ataxia, 3) willingness to participate, and 4) age 6 years 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 the Scale for Assessment and Rating of Ataxia (SARA) and other 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 till 2 years from the baseline visit or the end of August 2012, when the study was closed. In each visit, the severity of ataxia was recorded by a trained ataxia expert using SARA scores, which measure eight different domains of ataxia symptoms.<sup>19</sup> Comorbid medical conditions such as hypertension,

diabetes mellitus, congestive heart failure, and hyperlipidemia were collected.

### Genetic testing

DNA samples from blood of 263 participants were obtained and CAG repeat expansions were determined in S.M.P.'s laboratory.<sup>3</sup> Blood samples of thirty-seven patients were not available in the research laboratory; we used repeat numbers from commercial laboratories. In 19 patients, the information of CAG repeat expansions was not available (one SCA1, five SCA2, 10 SCA3, three SCA6).

### Predictor variables

CHA<sub>2</sub>DS<sub>2</sub>-VASc (clinical predictive score based on congestive heart failure, hypertension, age  $\geq 75$ , diabetes, prior stroke, vascular disease, age 65–74, sex category) is a scoring system for predicting the risk of stroke in patients with non-rheumatic atrial fibrillation (range: 0–9). The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is primarily used to determine whether anticoagulant treatment is required and has also been employed to predict stroke risks in patients without atrial fibrillation.<sup>20</sup> CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are calculated based on age, sex, history of congestive heart failure, hypertension, stroke or transient ischemic attacks or thromboembolism, vascular disease (peripheral artery disease, myocardial infarction, aortic plaques), and diabetes mellitus.<sup>21</sup> Higher scores indicate higher risks of developing a cerebrovascular event. Hyperlipidemia is a major cardiovascular risk but not included in the original version of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score; thus we took hyperlipidemia into account and developed modified CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. We used modified CHA<sub>2</sub>DS<sub>2</sub>-VASc scores to reflect vascular risk factors or cerebrovascular health.

### Outcome variables

SARA is our primary outcome, which measures motor performance in ataxia patients with a total score ranging from 0 to 40. SARA scores correspond with the visual analog scale (VAS score: 0–100) in a linear fashion and higher SARA scores reflect poor motor performance.<sup>19</sup> We also collected age at disease onset as another outcome to test if vascular risk factors would trigger earlier disease onset.

### Statistical analysis

Participants with repeated outcome measures were entered into analyses. SCA1, 2, 3, and 6 were treated as four independent cohorts and analyzed separately. We employed repeated measures linear regression (an exchangeable working within-subject correlation model via a generalized estimating equation [GEE]) to compute average rates of disease progression in each SCA group and to assess the associations between either CHA<sub>2</sub>DS<sub>2</sub>-VASc scores or modified CHA<sub>2</sub>DS<sub>2</sub>-VASc scores after controlling for age, sex, and pathological CAG repeat number. The longitudinal effects of vascular risk factors on disease progression during the 2-year observation period were assessed by entering the interaction terms (CHA<sub>2</sub>DS<sub>2</sub>-VASc scores  $\times$  time or modified CHA<sub>2</sub>DS<sub>2</sub>-VASc scores  $\times$  time) into the GEE models.

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

	SCA 1	SCA 2	SCA 3	SCA 6
<b>Demographic feature</b>				
Sample size, n	53	69	129	68
Mean age, years (SD)	50.3 (13.0)	50.9 (13.5)	51.4 (12.3)	65.5 (10.8)
Sex, M:F	24:29	29:40	62:67	30:38
White race, %	90.6	73.9	54.2	91.2
Mean age of onset (SD)	40.2 (11.7)	36.4 (11.9)	38.9 (11.9)	52.3 (10.4)
Mean disease duration (SD)	8.8 (6.9)	13.6 (8.3)	11.5 (7.8)	11.7 (10.5)
Median repeats (range)	46 (37–59)	39 (23–49)	71 (60–79)	22 (22–27)
	N=52	N=64	N=119	N=65
<b>Functional state</b>				
SARA score (SD)	14.4 (8.2)	17.1 (7.4)	15.1 (8.9)	14.1 (7.4)
			N=128	
<b>Vascular risk factors</b>				
CHA <sub>2</sub> DS <sub>2</sub> -VASc scores (SD)	0.4 (0.9)	0.7 (1.1)	0.7 (1.1)	1.6 (1.5)
	[0: 77%]	[0: 67%]	[0: 63%]	[0: 37%]
Modified CHA <sub>2</sub> DS <sub>2</sub> -VASc scores (SD)	0.5 (1.1)	0.8 (1.2)	0.8 (1.1)	1.8 (1.6)
	[0: 73%]	[0: 64%]	[0: 61%]	[0: 34%]
Abbreviations: CHA <sub>2</sub> DS <sub>2</sub> -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.				

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<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-VASc=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<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-VASc scores (Table 2).

## Discussion

In the present study, vascular risk factors indexed by CHA<sub>2</sub>DS<sub>2</sub>-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

	Regression Coefficient in GEE Models (outcome: SARA score)				Regression Coefficient in Linear Regression Models (outcome: age at onset)			
	SCA 1	SCA 2	SCA 3	SCA 6	SCA1	SCA2	SCA3	SCA6
CHA <sub>2</sub> DS <sub>2</sub> -VASc model								
Age, years	0.22	0.27*	0.51*	0.37*	0.76*	0.60*	0.61*	0.62*
Female	4.65*	-1.89	0.08	0.12	-1.84	-0.85	-0.22	-0.64
CAG repeat	0.36	1.05*	1.26*	2.26*	-0.07	-0.99*	-0.71*	-3.08*
CHA <sub>2</sub> DS <sub>2</sub> -VASc scores	-2.06	0.28	-0.12	-0.02	0.75	-0.84	0.07	-2.08
Time, minutes	0.14*	0.10*	0.07*	0.03				
CHA <sub>2</sub> DS <sub>2</sub> -VASc × time	-0.04	-0.04	-0.02	0.02				
Modified CHA <sub>2</sub> DS <sub>2</sub> -VASc model								
Age, years	0.23	0.27*	0.51*	0.41*	0.76*	0.64*	0.61*	0.57*
Female	4.63	-1.90	0.10	-0.05	-1.78	-1.14	-0.20	-0.29
CAG repeat	0.41	1.04*	1.26*	2.18*	-0.09	-1.02*	-0.71*	-3.03*
Modified CHA <sub>2</sub> DS <sub>2</sub> -VASc	-1.38	0.28	-0.08	-0.39	0.45	-1.59	0.16	-1.54
Time, minutes	0.14*	0.11*	0.07*	0.03				
Modified CHA <sub>2</sub> DS <sub>2</sub> -VASc × time	-0.02	-0.04	-0.02	0.02				

Abbreviations: CHA<sub>2</sub>DS<sub>2</sub>-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, CHA<sub>2</sub>DS<sub>2</sub>-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.

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