Brief Reports

Vascular Risk Factors and Clinical Progression in Spinocerebellar Ataxias

Raymond Y. Lo, Karla P. Figueroa, Stefan M. Puulst, Chi-Ying Lin, Susan Perlman, George Wilmot, Christopher M. Gomez, Jeremy Schmahmann, Henry Paulson, Vikram G. Shakkottai, Sarah H. Ying, Theresa Zesiewicz, Khalaf Bushara, Michael Geschwind, Guangbin Xia, S. H. Subramony, Tetsuo Ashizawa, & Sheng-Han Kuo

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, University of Utah, Salt Lake City, UT, USA, 5 Department of Neurology, Emory University, Atlanta, GA, USA, 6 Department of Neurology, University of Chicago, Chicago, IL, USA, 7 Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, 8 Department of Neurology, University of Michigan, Ann Arbor, MI, USA, 9 Department of Neurology, Johns Hopkins University, Baltimore, MD, USA, 10 Department of Neurology, University of South Florida, Tampa, FL, USA, 11 Department of Neurology, University of Minnesota, Minneapolis, MN, USA, 12 Department of Neurology, University of California, San Francisco, CA, 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 scores as 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

Citation: Lo RY, Figueroa KP, Puulst SM, et al. Vascular risk factors and clinical progression in spinocerebellar ataxias. Tremor Other Hyperkinet Mov. 2015; 5.

doi: 10.7916/D89885S0

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. The age of onset and disease progression in ataxia are inversely associated with the number of pathological CAG repeats. Polyglutamine repeat expansions cause defective protein quality control and mitochondrial dysfunction leading to neuronal death. 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.6-11

Cerebrovascular disease, atherosclerosis, hypertension, diabetes mellitus, and hyperlipidemia, are associated with vascular dementia and Alzheimer’s disease (AD). 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. 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. 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
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 mitochon-
drial 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. 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. 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

CHA2DS2-VASc (clinical predictive score based on congestive heart
failure, hypertension, age ≥ 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 CHA2DS2-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. CHA2DS2-
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, myo-
cardial infarction, aortic plaques), and diabetes mellitus. 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 CHA2DS2-VASc score; thus we took
hyperlipidemia into account and developed modified CHA2DS2-
VASc scores. We used modified CHA2DS2-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. 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 CHA2DS2-VASc scores or modified CHA2DS2-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 (CHA2DS2-VASc scores × time or
modified CHA2DS2-VASc scores × time) into the GEE models.
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 α-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 = 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 2. Effects of Vascular Risk Factors on Ataxia Progression and Onset in Regression Models

<table>
<thead>
<tr>
<th></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>CHA2DS2-VASc model</td>
<td></td>
<td></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>
<tr>
<td>Modified CHA2DS2-VASc model</td>
<td></td>
<td></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.
Vascular Risk Factors in Spinocerebellar Ataxias


1002/ana.410420615.


