Parkinsonism and Related Disorders xxx (2017) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Dystonia and ataxia progression in spinocerebellar ataxias

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ARTICLE INFO

Article history:
Received 23 June 2017
Received in revised form
3 October 2017
Accepted 9 October 2017

Keywords:
Spinocerebellar ataxia
Dystonia
Trinucleotide repeat
Modifier

ABSTRACT

Background: Dystonia is a common feature in spinocerebellar ataxias (SCAs). Whether the presence of dystonia is associated with different rate of ataxia progression is not known.
Objectives: To study clinical characteristics and ataxia progression in SCAs with and without dystonia.
Methods: We studied 334 participants with SCA 1, 2, 3 and 6 from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) and compared the clinical characteristics of SCAs with and without dystonia. We repeatedly measured ataxia progression by the Scale for Assessment and Rating of Ataxia every 6 months for 2 years. Regression models were employed to study the association between dystonia and ataxia progression after adjusting for age, sex and pathological CAG repeats. We used logistic regression to analyze the impact of different repeat expansion genes on dystonia in SCAs.
Results: Dystonia was most commonly observed in SCA3, followed by SCA2, SCA1, and SCA6. Dystonia was associated with longer CAG repeats in SCA3. The CAG repeat number in *TBP* normal alleles appeared to modify the presence of dystonia in SCA1. The presence of dystonia was associated with higher SARA scores in SCA1, 2, and 3. Although relatively rare in SCA6, the presence of dystonia was associated with slower progression of ataxia.
Conclusions: The presence of dystonia is associated with greater severity of ataxia in SCA1, 2, and 3, but predictive of a slower progression in SCA6. Complex genetic interactions among repeat expansion genes can lead to diverse clinical symptoms and progression in SCAs.

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https://doi.org/10.1016/j.parkreldis.2017.10.007
1353-8020/

1. Introduction

Spinocerebellar ataxias (SCAs) are a group of autosomal dominant cerebellar disorders, and among them SCA1, 2, 3, and 6 are the most common subtypes. In addition to ataxia, patients with SCA often have other movement disorders. Dystonia is one of the most common co-existing movement disorders in SCAs, especially in SCA3 [1–8]. The genetic underpinning for dystonia in SCAs has not been studied extensively. Although the pathological CAG repeat number per se is the major determinant [9], other repeat expansion genes also play a role in the onset age of ataxia, suggesting the underlying complex interaction among repeat expansion genes [10,11]. The presence of dystonia is also possibly driven by the complex gene-gene interaction and thus leads to diverse clinical presentations in SCAs.

The concept of clinical subtypes has been extensively studied in Parkinson's disease (PD), for which tremor-predominant PD is of slower disease progression than postural instability and gait difficulty (PIGD) predominant PD [12]. Besides, the clinical subtypes of SCA2, SCA3, and dentatorubral-pallidoluysian atrophy (DRPLA) had also been reported to predict the clinical presentation and prognosis [6,13,14]. Likewise, we hypothesize that dystonia in SCAs reflects a different underlying genetic complex and suggests a different rate of ataxia progression or prognosis. Therefore, we tested these hypotheses by studying cohort of SCA patients from the Clinical Research Consortium for SCAs (CRC-SCA), the largest longitudinal SCA cohort in the North America.

2. Patients and methods

2.1. Patient selection

Three hundred and forty-five SCA patients were enrolled in the natural history study of CRC-SCA [15], and the baseline characteristics and clinical progression had been investigated thoroughly in this cohort [15–19]. We excluded 11 patients without information on the dystonic symptom, so we analyzed on 334 patients. These patients were evaluated by ataxia specialists during January 2010 to August 2012, from 12 participating centers in the United States, including Columbia University, Emory University, Johns Hopkins University, Massachusetts General Hospital, University of California Los Angeles, University of California San Francisco, University of Chicago, University of Florida, University of Michigan, University of Minnesota, University of South Florida, and University of Utah. These SCA patients were either self-referred to ataxia clinics or referred by community physicians, local support groups, and the National Ataxia Foundation. The local institutional review boards approved the uniform study protocol and informed consents were obtained from all participants. The inclusion criteria were the following: (1) the presence of ataxia, (2) definite genetic diagnosis of SCA1, 2, 3, or 6 either for the subject or affected family members with ataxia, (3) willingness of participation, and (4) age of 6 years and older. The exclusion criteria were the following: (1) known recessive, X-linked, or mitochondrial ataxia, (2) exclusion of SCA1, 2, 3, and 6 by genetic tests, and (3) concomitant disorders that affect ataxia measurement used in this study.

Every patient received face-to-face interviews and neurological examinations by ataxia specialists, and the presence of dystonia was determined at the baseline clinical visit. All our ataxia specialists were well trained neurologists, and they were experts in the field of ataxia and movement disorders. During the neurological examination, dystonia was recognized by the sustained movement, either twisting or repetitive, with co-contraction of agonists and antagonists, and the movement might progress to prolonged abnormal posture [20–22]. We examined patients at rest, action, and walking, and we looked for twisted or repetitive pattern of dystonia in different body parts including face, neck, arms, legs and trunk [20–22]. Specifically, action dystonia of the hands was evaluated with the repeated finger-nose maneuver and also with holding the arms stretched while sitting for 10 s. The age of onset was defined as the age when the patient first noted gait ataxia during walking in ordinary circumstances. All participants were asked to provide their blood samples for SCA genotyping. The studied subjects were followed every six months until two years from the baseline visit or until 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) [23].

2.2. Genetic testing

DNA samples from blood were obtained from subjects, and the repeat expansions of the 9 genes, including *ATXN1* (SCA1), *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNA1A* (SCA6), *ATXN7* (SCA7), *ATXN10* (SCA10), *PP2R2B* (SCA12), *TBP* (SCA17), and *FRDA* (Friedreich's ataxia, FA), were determined in Dr. Stefan Pulst's laboratory. The Qiagen FlexiGene DNA Kit (Qiagen, Hilden, Germany) was used to extract DNA and repeat expansions were determined by multiplex polymerase chain reaction (PCR), followed by capillary electrophoresis with internal standards. Re-genotyping and Sanger sequencing were performed for verification of repeat length in 10% of all samples.

2.3. Predictive variables

Dystonia was treated as a dichotomous variable or major predictor [19]. The repeat numbers of 9 genes specified above were entered into the model to test whether the presence of dystonia was influenced by other SCA repeat expansion genes. Since there are two alleles in each gene, we chose the longer repeat allele for our analyses.

2.4. Outcome variables

We used SARA to measure the severity of ataxia symptoms. SARA ranges from 0 to 40, and higher SARA scores reflected worse motor performance. This outcome measure was treated as continuous variables. The presence of dystonia as a dichotomous variable was the outcome measurement when testing the gene-gene complex interaction.

2.5. Statistical analysis

SCA 1, 2, 3, and 6 were treated as four independent cohorts and analyzed independently. We separated each type of SCAs into two groups, depending on whether they had dystonia or not at baseline.

We used Chi-square tests to compare the percentage of SCAs with dystonia. We assessed whether demographic features of patients with SCAs were normally distributed by Kolmogorov–Smirnov test. For normally distributed variables, we used Student's t-test, and for non-normally distributed variables, we used the Mann–Whitney *U* test for the comparison of basic demographics.

We employed logistic regression to investigate whether different SCA repeat expansion genes would influence the presence of dystonia in SCAs. These methods have been used extensively in genetic modification studies for SCAs [6,11].

The longitudinal analyses of ataxia progression of the two SCA groups (dystonia vs. non-dystonia) during the 2-year observation were conducted by entering the interaction terms (dystonia x time)

Please cite this article in press as: P.-H. Kuo, et al., Dystonia and ataxia progression in spinocerebellar ataxias, Parkinsonism and Related Disorders (2017), https://doi.org/10.1016/j.parkreldis.2017.10.007