Parkinsonism and Related Disorders 22 (2016) 87–92

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Depression and clinical progression in spinocerebellar ataxias

Raymond Y. Lo [a], Karla P. Figueroa [b], Stefan M. Pulst [b], Susan Perlman [c], George Wilmot [d], Christopher Gomez [e], Jeremy Schmahmann [f], Henry Paulson [g], Vikram G. Shakkottai [g], Sarah Ying [h], Theresa Zesiewicz [i], Khalaf Bushara [j], Michael Geschwind [k], Guangbin Xia [l], Jui-Tsen Yu [m], Lue-En Lee [m], Tetsuo Ashizawa [l], S.H. Subramony [l], Sheng-Han Kuo [m, *]

[a] Department of Neurology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan
[b] Department of Neurology, University of Utah, Salt Lake City, UT, USA
[c] Department of Neurology, University of California, Los Angeles, CA, USA
[d] Department of Neurology, Emory University, Atlanta, GA, USA
[e] Department of Neurology, University of Chicago, Chicago, IL, USA
[f] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[g] Department of Neurology, University of Michigan, Ann Arbor, MI, USA
[h] Department of Neurology, Johns Hopkins University, Baltimore, MD, USA
[i] Department of Neurology, University of South Florida, Tampa, FL, USA
[j] Department of Neurology, University of Minnesota, Minneapolis, MN, USA
[k] Department of Neurology, University of California, San Francisco, CA, USA
[l] Department of Neurology and McKnight Brain Institute, University of Florida, Gainesville, FL, USA
[m] Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

ARTICLE INFO

Article history:
Received 8 October 2015
Received in revised form
4 November 2015
Accepted 17 November 2015

Keywords:
Depression
Cerebellum
Spinocerebellar ataxias
Suicide
Neurodegeneration

ABSTRACT

Background: Depression is a common comorbidity in spinocerebellar ataxias (SCAs) but its association with ataxia progression is not well understood.
Objectives: To study the prevalence and influence of depressive symptoms in SCAs.
Methods: We studied 300 participants with SCA 1, 2, 3 and 6 from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) and repeatedly measured depressive symptoms by the 9-item Patient Health Questionnaire (PHQ-9) along with other clinical features including ataxia, functional status, and quality of life every 6 months for 2 years. We employed regression models to study the effects of depressive symptoms on clinical progression indexed by Scale for Assessment and Rating of Ataxia (SARA), Unified Huntington's Disease Rating Scale Part IV (UHDRS-IV) and EQ5D after adjusting for age, sex and pathological CAG repeats.
Results: Comorbid depression is common in SCAs (26%). Although the baseline prevalence of depression was similar among different SCA types, suicidal ideation was more frequently reported in SCA3 (65%). Depressive symptoms were associated with SARA scores but did not significantly progress over time within 2 years or deteriorate by increased numbers of pathological CAG repeats. The effects of depression on ataxia progression varied across different SCA types. Nevertheless, depression had consistently negative and significant impact on functional status and quality of life in all SCAs, even after accounting for ataxia progression.
Conclusions: Depressive symptoms are not simply the consequence of motor disability in SCAs. Comorbid depression per se contributes to different health outcomes and deserves more attention when caring patients with SCAs.

1. Introduction

Spinocerebellar ataxias (SCAs) are a group of autosomal-dominant cerebellar degenerative disorders with SCA 1, 2, 3, and 6 as the most common types [1,2]. In addition to adult-onset

* Corresponding author. 650 West 168th Street, Room 305, New York, NY, 10032, USA.
E-mail address: sk3295@columbia.edu (S.-H. Kuo).

http://dx.doi.org/10.1016/j.parkreldis.2015.11.021
1353-8020/

progressive cerebellar ataxia, other motor features such as pyramidal signs and eye movement disorders are also often associated with SCAs [3]. Pathological CAG repeat expansions are the major genetic underpinning and the encoded polyglutamine aggregates are found in neurons of SCA brains [4]. The age of ataxia onset and the rate of disease progression are inversely associated with the number of pathological CAG repeats [1,2,5], indicating that the toxic effects of polyglutamine proteins and/or the repeat associated non-ATG translation products increase with longer repeat expansions [6]. The pathological CAG repeats, however, only explain 50–70% of the variability of the age of onset in SCAs [7–9], suggesting that factors other than CAG repeats may play a role in clinical progression in SCAs.

Depression is a common comorbidity in neurodegenerative disorders, such as Parkinson's disease (PD) [10] and Huntington's disease (HD) [11], and is thought to arise from neurodegeneration in the depression-related brain circuitry in these disorders. Depressive symptoms could even precede the motor impairment in PD and HD, arguing against that depression merely results from motor disability. Likewise, patients with SCA often have depressive symptoms [12]. Some studies report that depression is more frequently seen in SCA3 than other SCAs [13–15], but this finding is not consistently shown in others [12,16]. Depression has been proposed to be part of the neurodegeneration in SCAs [17–19], as cerebellum has dense connections with frontal lobes and multiple brainstem regions and cerebellar degeneration may lead to cognitive impairment and emotional disturbance, namely cerebellar cognitive affective syndrome [20]. Comorbid depression in SCA may indicate that the network involving cerebellum and limbic system is preferentially affected and thus the course of ataxia progression is likely different. The notion that non-motor symptoms may contribute to the motor deterioration has been extensively studied in HD [21] and PD [22], but not in SCAs yet.

The prevalence of depression in SCAs has been reported in a large cohort of SCA patients in EUROSCA, as defined by the 9-item Patient Health Questionnaire (PHQ-9) $\geq$ 10: 24.5% in SCA1, 20.3% in SCA2, 25.2% in SCA3, and 17.8% in SCA6 [12], which are similar to studies of fewer SCA patients in various populations [13–18,23]. However, few studies repeatedly measured depression together with ataxia severity in a longitudinal setting, and these studies were often hindered by small sample size [24,25]. Therefore, we used the longitudinal dataset from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) to investigate the prevalence of depression and how depressive symptoms evolve along with ataxia progression, functional status and quality of life in SCA 1, 2, 3, 6 during 2-year follow-ups.

2. Methods

2.1. Study subjects

The study participants were recruited by ataxia or movement disorders specialists during July 2009–May 2012 from 12 CRC-SCA centers [1]. These patients were referred to specialty clinics by patients themselves, community physicians, local support groups and the National Ataxia Foundation. The uniform study protocol was approved by the local institutional review boards and the 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 another affected family member with ataxia, 3) willingness of participation, and 4) age of 6 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 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 until 2 years from the baseline visit or 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) and the Unified Huntington's Disease Rating Scale part IV (UHDRS-IV), and assessed depressive symptoms by PHQ-9 during the interview [1,26,27].

2.2. Genetic testing

DNA samples from blood of 263 participants were obtained and CAG repeat expansions were determined in Dr. Stefan Pulst's laboratory. For 37 patients whose blood samples were not available in the research lab, we used the repeat numbers from the commercial labs. In 19 patients, the information of CAG repeat expansion was not available (one SCA1, five SCA2, ten SCA3, three SCA6).

2.3. Predictor variables

We used PHQ-9 scores to reflect the severity of depressive symptoms. The PHQ-9 consists of nine questions to assess depressive mood over the past 2 weeks. Four levels were rated (not at all = 0; several days = 1; more than half the days = 2; nearly every day = 3) in each question, and higher scores (range, 0–27) reflect the severity of depression. PHQ-9 has been extensively studied as a tool to measure the severity of depression: none (0–4), mild (5–9), moderate (10–14), and severe ($\geq$15) [28]. We defined clinically relevant depression as PHQ-9 $\geq$ 10, a commonly used and extensively validated cut-off point in previous studies [29]. Suicidal ideation was defined as scoring >0 in item 9 of PHQ-9: thoughts that you would be better off dead or of hurting yourself in some ways in the past 2 weeks, which have been extensively studied in primary care patients [30,31].

2.4. Outcome variables

Although PHQ-9 was our major predictor for ataxia progression, we also examined factors that might affect PHQ-9, including ataxia severity, in a way to address the likely interaction or the causal effects in both directions. SARA was our outcome of interest, which measures 8 domains of motor performance in ataxia patients with a total score ranging from 0 to 40. Higher SARA scores reflected poor motor performance. There were 25 questions regarding functional performance in daily activities in UHDRS-IV. One point was given if the answer to the individual question was positive; the total score of UHDRS-IV ranged from 0 to 25, and higher scores indicated better functional status. EQ-5D was a standard instrument to measure health related quality of life. Two health outcome indicators were employed in the study: EQ-5D index score and EQ-VAS score. EQ-5D index was to score the best condition of the day (no problems = 1, moderate problems = 2, severe problems = 3) in 5 domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, with a total score ranging from 3 to 15. EQ-VAS score was estimated by asking participants his/her health state of the day of the visit with a visual analogue scale from 0 = worst imaginable to 100 = best imaginable.

2.5. Statistical analysis

We compared the prevalence of baseline clinical relevant depression (PHQ9 $\geq$ 10) and suicidal ideation (PHQ-9 question 9 score > 0) in different SCA types using analysis of variance. We employed repeated measures linear regression (an exchangeable working within-subject correlation model via a generalized