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Abnormal corticospinal tract function and motor cortex excitability in non-ataxic SCA2 mutation carriers: A TMS study

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HIGHLIGHTS

- TMS markers of corticospinal tract integrity are altered in non-ataxic SCA2 mutation carriers.
- Motor thresholds are elevated, and cortical silent periods and CMCT are prolonged.
- CMCT correlates directly with CAG repeat length, and inversely with predicted time to ataxia onset.

ABSTRACT

Objective: To evaluate if the corticospinal tract is affected in the prodromal stage of spinocerebellar ataxia type 2 (SCA2), prior to development of the cerebellar syndrome.
Methods: A cross-sectional study was conducted in 37 non-ataxic SCA2 mutation carriers and in age- and sex-matched healthy controls. All subjects underwent clinical assessment and transcranial magnetic stimulation to determine corticospinal tract integrity to the right abductor pollicis brevis and tibialis anterior muscles.
Results: Non-ataxic SCA2 mutation carriers showed significantly higher resting and active motor thresholds for both muscles, and prolonged cortical silent periods and central motor conduction times (CMCT), compared to controls. CMCT to the tibialis anterior correlated directly with CAG repeat size, and inversely with predicted time to ataxia onset.
Conclusion: Findings provide novel electrophysiological evidence for affection of the corticospinal tract and motor cortex in prodromal SCA2. Slowed conduction in the corticospinal tract to the lower limbs reflects polyglutamine neurotoxicity, and predicts time to ataxia onset.
Significance: Identification of corticospinal tract damage and decreases motor cortical excitability in the prodromal stage of SCA2 allows early disease monitoring. This will become important as soon as effective neuroprotective treatment will be available.

1. Introduction

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant cerebellar ataxia that belongs to the group commonly referred to as 'polyglutaminopathies' since it is caused by expansion of CAG repeats coding for polyglutamine (polyQ) stretches (Auburger, 2012). The SCA2 gene is located on chromosome 12q24.1 and its product, designated as ataxin-2, seems to play key roles in the RNA metabolism. With abnormal polyQ expansions, this protein acquires toxic functions leading to progressive cell death in neural tissues, predominantly in the Purkinje cell layer in the cerebellum (Pulst et al., 1996). The disease has the highest worldwide prevalence in Cuba, where a founder effect has been invocated (Auburger et al., 1990; Velazquez-Perez et al., 2009a). Almost 600 SCA2 patients and 8000 at-risk individuals live in Cuba, which yields an estimated ataxin-2 mutation prevalence of nearly 20 cases per 100,000 inhabitants in the whole country and 183 cases

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per 100,000 inhabitants in the Holguin province (Velázquez-Pérez et al., 2011).

SCA2 patients exhibit a wide range of clinical manifestations including gait ataxia, postural instability, dysmetria and dysdiadochokinesia. Usually, these cerebellar features are accompanied by slowing of horizontal saccades, peripheral sensorimotor neuropathy, cognitive disorders, sleep abnormalities, dysautonomia and signs of corticospinal tract involvement (Velázquez-Pérez et al., 2009b; Orozco Diaz et al., 1990). Most of these clinical abnormalities precede the cerebellar syndrome onset, representing possible preclinical biomarkers (Jacobi et al., 2013; Velázquez-Pérez et al., 2009, 2014a,b, 2016a; Rodríguez-Labrada et al., 2011). Their identification is a focus of current research due to their importance for clinical trials that target slowing or prevention of the neurodegenerative process. However, corticospinal tract involvement has not been extensively studied in prodromal stages of SCA2. The available clinical evidence for corticospinal tract involvement has been derived from cross-sectional and follow-up studies of the Cuban population of non-ataxic SCA2 mutation carriers that revealed hyperreflexia in 30–45% of the cases (Velázquez-Pérez et al., 2014a,b). Electrophysiological assessment of corticospinal tract integrity by transcranial magnetic stimulation (TMS) has not been employed in prodromal SCA2.

TMS is a widely used non-invasive neurophysiological technique able to assess painlessly and safely the integrity of the corticospinal tract, and it has proved its utility as diagnostic tool in many neurodegenerative diseases such as multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease and spinocerebellar ataxias (Chen et al., 2008; Kobayashi and Pascual-Leone, 2003; Schwenkreis et al., 2002; Groppa et al., 2012). Earlier TMS studies in clinically manifest SCA2 patients have revealed increased motor thresholds, prolonged central motor conduction times (CMCT), and prolonged cortical silent period (CSP) durations (Restivo et al., 2000, 2002, 2004).

In order to evaluate if these TMS abnormalities appear prior to development of the cerebellar syndrome in SCA2, we assessed these TMS measures in the present study in 37 non-ataxic SCA2 mutation carriers and, for comparison, in gender- and age matched healthy controls. Parts of this study have been published in a letter (Velazquez-Perez et al., 2016b)

2. Methods and materials

2.1. Participants

Forty-five non-ataxic SCA2 mutation carriers were screened in the Center for the Research and Rehabilitation of Hereditary Ataxias in Holguín during the period between November 2014 and May 2015 for eligibility to participate in this study. The following inclusion criteria had to met: (a) absence of definite cerebellar syndrome; (b) CAG expansion >32 repeats in the ataxin-2 gene; (c) age between 18 and 70 years. Exclusion criteria were: other diseases affecting the nervous system, psychiatric disorders, chronic alcohol abuse, pregnancy and use of CNS-active drugs influencing TMS measures of motor cortex excitability (Ziemann et al., 2015). 37 non-ataxic SCA2 mutation carriers (mean age ± SD, 40.4 ± 11.0 years, range 18–70 years; 11 male; mean polyglutamine repeat size, 36.30 ± 2.31) could be included. 37 healthy volunteers belonging to non-SCA2 families (mean age 40.38 ± 11.25 years, range 19–71 years) served as age- and sex-matched controls. The Ethics Committee of the National Center of Ataxia approved the study. Written informed consent was obtained from all participants prior to study enrolment.

All participants underwent the same clinical and electrophysiological assessments, following standardized and validated procedures.

2.2. Clinical assessments

All subjects were evaluated clinically following the standardized Mayo Clinic procedures for neurological examination and structured medical interview. Evaluation of cerebellar signs was performed using the Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al., 2006), while non-cerebellar features were assessed with the Inventory of Non-Ataxia Symptoms scale (INAS) (Schmitz- Hübsch et al., 2008).

2.3. Electrophysiological assessments

2.3.1. Transcranial magnetic stimulation (TMS)

Motor-evoked potentials (MEPs) were obtained using an STM-900 2.4 tesla magnetic stimulator (STM-900, ATES-MEDICA, Italy) to deliver TMS over motor cortex. For the upper limb, the stimuli were applied through a 12.5 cm outside diameter circular coil positioned tangential to the scalp with its center 30 mm lateral to the vertex over the left hemisphere. MEPs were recorded from the right abductor pollicis brevis (APB) muscle using Ag–AgCl surface electrodes and stored on an EMG device (Neuronica 5-UC; IC Neuronic S.L; Cuba) for offline analysis. For the lower limb, TMS was applied to the scalp with the center of the coil over the vertex and MEPs were recorded from the right tibialis anterior (TA) muscle. The current waveform was biphasic, and the current direction in the coil was counterclockwise for the second phase of the pulse for preferential excitation of the left hemisphere.

Subjects were seated in a comfortable reclining chair. The EMG was recorded with a bandpass filter of 5 Hz–3 kHz, sweep duration of 10–50 ms/division, gain of 0.05–2.5 mV/division and sampling rate of 5 kHz. A ground electrode was placed proximally to the recording site. The following TMS measures were obtained:

2.3.2. Motor thresholds

Resting motor threshold (RMT) was determined at rest using the relative frequency method (Groppa et al., 2012) and defined as the minimum intensity required to elicit MEPs of $\geqslant 50\ \mu V$ in peak-to-peak amplitude in at least five out of ten trials. Muscle relaxation was controlled acoustically. Active motor threshold (AMT) was determined during slight voluntary target muscle contraction by either performing a pincer grip with thumb and index finger, when recording from the APB, or slight dorsiflexion of the foot when recording from the TA. The AMT was defined as the minimum intensity required to elicit MEPs of $\geqslant 200\ \mu V$ in at least five out of ten trials.

2.3.3. MEP latency and MEP amplitude

TMS was applied with an intensity of 120% RMT and, in addition, with an intensity of 100% of maximum stimulator output. At both intensities, the MEPs were recorded at rest and during slight voluntary target muscle contraction. Three trials were performed for each condition and the MEP onset latency and peak-to-peak amplitude were analyzed from the single trials.

2.3.4. Cortical silent period (CSP)

CSP was evoked applying TMS of 120% RMT while the participants were contracting the target muscles with maximal force. The duration of the CSP was measured from the end of the MEP until the first re-occurrence of voluntary EMG activity. Five trials were performed and the CSP duration was calculated as mean from the single trial data.