Clinical Neurophysiology 129 (2018) 895–900

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Progression of corticospinal tract dysfunction in pre-ataxic spinocerebellar ataxia type 2: A two-years follow-up TMS study

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ARTICLE INFO

Article history:
Accepted 23 January 2018
Available online 15 March 2018

Keywords:
Spinocerebellar ataxia type 2
Pre-ataxic disease stage
Corticospinal tract
Transcranial magnetic stimulation
Central motor conduction time
Biomarker
Disease progression

HIGHLIGHTS

- Investigation of progression of corticospinal tract (CST) dysfunction in pre-ataxic SCA2 using TMS.
- Pre-ataxic SCA2 showed significant progression of CST dysfunction over 2-years follow-up.
- TMS measures of CST dysfunction may have utility for disease monitoring in pre-ataxic SCA2.

ABSTRACT

Objective: Corticospinal tract (CST) dysfunction is common in the pre-ataxic stage of spinocerebellar ataxia type 2 (SCA2) but quantitative assessment of its progression over time has not been explored. The aim of this study was to quantify the progression of CST dysfunction in pre-ataxic SCA2 using transcranial magnetic stimulation (TMS).
Methods: Thirty-three pre-ataxic SCA2 mutation carriers and a 33 age- and gender-matched healthy controls were tested at baseline and 2-years follow-up by standardized clinical exams, validated clinical scales, and TMS.
Results: Pre-ataxic SCA2 mutation carriers showed a significant increase of resting motor thresholds (RMT) to abductor pollicis brevis (APB) and tibialis anterior (TA) muscles, and of central motor conduction time (CMCT) to TA at 2-years follow-up, over and above changes in healthy controls. The changes in the pre-ataxic SCA2 mutation carriers were independent of the presence of clinical signs of CST dysfunction at baseline, and independent of conversion to clinically definite SCA2 at 2-years follow-up.
Conclusions: TMS markers of CST dysfunction progress significantly during the pre-ataxic stage of SCA2.
Significance: TMS measures of CST dysfunction may provide biomarkers of disease progression prior to clinical disease expression that have potential utility for monitoring neuroprotective therapies in future clinical trials.

1. Introduction

Spinocerebellar ataxia type 2 (SCA2) is a severe and progressive autosomal dominant cerebellar ataxia caused by a dynamic mutation in the ATXN2 gene, consisting of an abnormal expansion of cytosine-adenine-guanine (CAG) triplets in the first codon of the gene, and leading to expression of long polyglutamine (PolyQ)

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https://doi.org/10.1016/j.clinph.2018.01.066
1388-2457/

stretches in the ataxin-2 protein (Auburger, 2012; Pulst et al., 1996). This protein seems to have global effects on mRNA metabolism, as well as on endocytosis, calcium signaling and control of metabolism and energy balance. The presence of an expanded PolyQ tract likely causes conformational changes in ataxin-2 resulting in gain and/or partial loss of function, leading to cellular dysfunction and neuronal cell death, which is most evident in the cerebellum, pons, basal ganglia and cerebral cortex (Auburger et al., 2017).

Clinically, the disease is characterized by ataxia of gait, postural instability, dysmetria, cerebellar dysarthria and dysdiachokinesia. Non-cerebellar features are slowing of horizontal saccadic eye movements, peripheral neuropathy, dysautonomia, cognitive dysfunction, sleep disturbances and signs of motor neuron involvement (Velazquez-Perez et al., 2011, 2017).

SCA2 is the second most frequent autosomal dominant cerebellar ataxia worldwide, but reaches the highest prevalence rates in Cuba where almost 600 SCA2 living patients and almost 8000 asymptomatic at-risk individuals are reported as a result of a founder effect in the Holguín province (Velazquez-Perez et al., 2009a).

Unfortunately, there exist as of yet no effective neuroprotective treatments against SCA2, although symptomatic therapies are available (Velazquez-Perez et al., 2011). However, recent pre-ataxic trials in SCA2 mouse models have revealed promising neuroprotective options for humans using antisense oligonucleotide therapy (Scoles et al., 2017). This prospective will require outcome measures that can objectively assess the effects of these treatments, in particular in pre-ataxic stages, when the degenerative changes are still incipient and the available clinical scales not sensitive to change (Maas et al., 2015).

Since we have previously reported the usefulness of transcranial magnetic stimulation (TMS) to provide surrogate biomarkers of CST dysfunction in pre-ataxic SCA2 by means of a cross-sectional approach (Velazquez-Perez et al., 2016a, 2016b), we sought here to study the changes of these alterations in 33 pre-ataxic SCA2 mutation carriers in a 2-years longitudinal study.

2. Methods and materials

2.1. Subjects

Thirty-three pre-ataxic SCA2 mutation carriers (23 female and 10 male) and 33 sex- and age-matched healthy controls were included in the present study at the Centre for the Research and Rehabilitation of Hereditary Ataxias. The pre-ataxic SCA2 mutation carriers had to meet the following inclusion criteria: (a) absence of definite cerebellar syndrome (SARA score $\leq$2); (b) CAG expansion $\geq$32 repeats in the ataxin-2 gene and (c) age between 18 and 70 years. Exclusion criteria for all participants 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). Finally, the healthy controls were carefully screened for the absence of ataxia in the family history, and absence of signs of ataxia in the neurological examination.

The mean age at baseline was 40.5 years (range: 21–70; standard deviation [SD]: 10.8) for the pre-ataxic SCA2 mutation carriers and 43.6 years (range: 19–71; SD: 12.0) for the controls. The mean expanded CAG repeat size for the pre-ataxic SCA2 mutation carriers was 36.2 (range: 32–44; SD: 2.3). The predicted age of onset of ataxia varied from 23 to 69 years (mean 53.3; SD: 11.2) and was estimated from each CAG repeat length between 34 and 39 repeats, using a survival analyses model obtained in a large population of 924 Cuban SCA2 patients and non-ataxic SCA2 mutation carriers (Almaguer-Mederos et al., 2010). Finally, the predicted mean time to ataxia onset was 13.6 years (range: −4 to 38; SD: 10.4).

All subjects were evaluated two times, at baseline, and approximately two years later (mean 1.95 years; range: 0.92–2.58; SD: 0.28). The experimental procedures conformed to the ethical standards of the committee on human experimentation of the Centre for the Research and Rehabilitation of Hereditary Ataxias in Holguín. All participants gave their written informed consent prior to study enrolment. The study was conducted in full accordance with the most recent version of the declaration of Helsinki.

2.2. Clinical assessments

At both time points, all participants were clinically tested following the standardized Mayo Clinic procedures for neurological examination (Denny-Brown et al., 1982) and structured medical interview. The Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al., 2006) was performed to evaluate cerebellar signs, while non-cerebellar features were assessed using the Inventory of Non-Ataxia Symptoms scale (INAS) (Schmitz-Hübsch et al., 2008). Conversion from pre-ataxic SCA2 to clinical definitive SCA2 at 2-years follow-up was based on development of a SARA score of $\geq$3 (Maas et al., 2015; Schmitz-Hübsch et al., 2006).

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 (ATES-MEDICA, Italy) to deliver TMS over motor cortex. The current waveform was biphasic (pulse duration, 250 μs), and the current direction in the coil was counterclockwise for the second phase of the pulse for preferential excitation of the left hemisphere (Sommer et al., 2006). In accord with the practical guidelines for diagnostic TMS of the International Federation of Clinical Neurophysiology (Groppa et al., 2012) TMS was applied through a circular coil (outer diameter, 12.5 cm) held tangential to the scalp with its center in the midline and 0–1 cm anterior to the vertex to target the presumable location of the hand representation in the left primary motor cortex 5–6 cm lateral and 1 cm anterior to the vertex. 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 with the center of the coil 5–6 cm anterior to the vertex to target the leg representation in motor cortex 1–2 cm posterior to the vertex, and MEPs were recorded from the right tibialis anterior (TA) muscle. 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 (Velazquez-Perez et al., 2016a)." The following TMS measures were obtained.

2.3.2. Resting motor threshold (RMT)

RMT was determined with a resolution of 5% of maximum stimulator output, using the relative frequency method (Rossini et al., 2015), with the target muscle voluntarily relaxed. It was defined as the minimum stimulation intensity to elicit MEPs of $\geq$50 μV in peak-to-peak amplitude in $\geq$5 out of 10 consecutive trials. Full target muscle relaxation was controlled by acoustic feedback of the EMG signal.