Clinical Neurophysiology 127 (2016) 3418–3424

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Motor cortical dysfunction develops in spinocerebellar ataxia type 3

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ARTICLE INFO

Article history:
Accepted 7 September 2016
Available online 15 September 2016

Keywords:
Spinocerebellar ataxia type 3
Corticomotoneuron
Transcranial magnetic stimulation

HIGHLIGHTS

- Cortical dysfunction is an early feature of SCA3 and associated with motor symptoms and ataxia.
- Identifying cortical neuronal dysfunction in SCA3 may be of therapeutic significance.
- SCA3 onset is not confined to the cerebellum and brainstem.

ABSTRACT

Objective: Spinocerebellar ataxia type 3 (SCA3) is an inherited neurodegenerative disorder characterized by cerebellar ataxia and variable expression of clinical features beyond the cerebellum. To gain further insights into disease pathophysiology, the present study explored motor cortex function in SCA3 to determine whether cortical dysfunction was present and if this contributed to the development of clinical manifestations.
Methods: Clinical phenotyping and longitudinal assessments were combined with central (threshold-tracking transcranial magnetic stimulation) and peripheral (nerve excitability) techniques in 11 genetically characterized SCA3 patients.
Results: Short-interval intracortical inhibition was significantly reduced in presymptomatic and symptomatic SCA3 patients ($-1.3 \pm 1.4\%$) compared to healthy controls ($10.3 \pm 0.7\%$, $P < 0.0005$), with changes evident prior to clinical onset of ataxia and related to worsening severity ($R = -0.78$, $P < 0.005$). Central motor conduction time was also significantly prolonged in presymptomatic and symptomatic SCA3 patients (7.5 ± 0.4 ms) compared to healthy controls (5.3 ± 0.2 ms, $P < 0.0005$) and related to clinical severity ($R = 0.81$, $P < 0.005$). Markers of peripheral motor neurodegeneration and excitability did not correlate with cortical hyperexcitability or ataxia.
Conclusions: Simultaneous investigation of clinical status, and central and peripheral nerve function has identified progressive cortical dysfunction in SCA3 patients related to the development of ataxia.
Significance: These findings suggest alteration in cortical activity is associated with SCA3 pathogenesis and neurodegeneration.

1. Introduction

Spinocerebellar ataxia type 3 (SCA3) is an autosomal dominant neurodegenerative disease and the most common hereditary spinocerebellar ataxia. Also known as Machado–Joseph disease, there is a wide spectrum of clinical expression in addition to ataxia, that may include progressive external ophthalmoplegia, dysarthria, dysphagia, pyramidal disturbances, dystonia, parkinsonism, sleep disorders, rigidity, peripheral neuropathy and distal muscle atrophy, suggestive of neurodegeneration beyond that originally described in the cerebellum and brainstem (Boller and Segarra, 1969; Pogacar et al., 1978; Rosenberg, 1992). Symptoms usually begin between the ages of 20 and 50 years and loss of motor control is ultimately so severe that survival is limited to 15–30 years following clinical onset. SCA3 presents clinically when neuronal loss within the cerebellum and brainstem has become advanced and irreversible, emphasizing the need to further understand pathophysiological processes, particularly the detection of early neuronal dysfunction, such that therapeutic strategies may be directed at earlier stages of disease.

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http://dx.doi.org/10.1016/j.clinph.2016.09.005
1388-2457/

SCA3 is caused by an unstable expansion of CAG triplet repeats in the ataxin-3 (*ATXN3*) gene on chromosome 14, resulting in an abnormal expanded polyglutamine repeat in the ubiquitously expressed ATXN3 protein, which makes the protein highly susceptible to misfolding and aggregation (Kawaguchi et al., 1994). Abnormalities beyond the cerebellum and brainstem have been demonstrated with neuroimaging and neuropathological studies to reveal neurodegeneration affecting the thalamus, and frontal, temporal, limbic, parietal and occipital lobes (D'Abreu et al., 2012; de Rezende et al., 2015). In addition, loss of motor neurons in the spinal cord and has been established, and may be associated with muscle cramps, amyotrophy and fasciculations, such that SCA3 may be regarded as a chronic motor neurone disorder (Kinoshita et al., 1995; Franca et al., 2008).

Although the mechanisms by which the misfolded ATXN3 protein induces motor neuron toxicity in SCA3 remain elusive, impairment of axonal transport, oxidative stress, neuronal signaling and RNA toxicity have all been reported (Li et al., 2015). Importantly, the mutant ATXN3 protein, which appears to be sequestered ubiquitously within the central nervous system, may induce neuronal hyperexcitability, which in turn may mediate the underlying pathogenesis in SCA3 (Jeub et al., 2006; Chen et al., 2008; Shakkottai et al., 2011). The impact of mutant ATXN3 on motor neurone function throughout the cortex and spinal cord remains to be fully elucidated and is of pathophysiological and therapeutic importance. Perhaps of relevance, cortical dysfunction has been linked to neurodegeneration in amyotrophic lateral sclerosis (Vucic and Kiernan, 2006; Vucic et al., 2008). Recently, the application of threshold tracking transcranial magnetic stimulation (TMS) techniques has enabled the early detection of upper motor neuron dysfunction (Menon et al., 2015). As such, the present study utilized clinical assessments combined with cortical and peripheral nerve assessment to further clarify the processes involved in neurodegeneration in SCA3.

2. Methods

Clinical phenotyping and assessment was combined with conventional and specialized neurophysiological assessments in 11 patients with genetically confirmed SCA3. A subset of presymptomatic SCA3 patients and symptomatic SCA3 patients with mild to moderate disease and duration less than 10 years were followed longitudinally for up to 36 months to characterize progression. Diagnosis was confirmed by DNA testing showing an expanded CAG repeat in the *ATXN3* gene on chromosome 14q32.1 in all patients. All patients gave informed consent to the procedures, which were approved by the South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committee.

SCA3 patients underwent clinical assessments of cerebellar ataxia using the International Cooperative Ataxia Rating Scale (ICARS), a 100-point semi quantitative scale that provides a total score (0–100) and four subscores: posture and stance (0–34), kinetic cerebellar function (0–52), dysarthria (0–8) and oculomotor dysfunction (0–6) (Trouillas et al., 1997). Greater scores indicate worsening cerebellar ataxia. The Total Neuropathy Scale-clinical version (TNSc) (Cornblath et al., 1999), was also assessed for each patient. The TNSc combines information obtained from grading of symptoms and signs to clinically quantify neuropathy and includes seven categories with severity rankings from 0 (none) to 4 (very severe): sensory symptoms; motor symptoms; autonomic symptoms; pinprick sensibility; vibration sensibility (128-Hz tuning fork); strength; and deep tendon reflexes (total score 0–28). Muscle strength was clinically assessed using the MRC for abductor pollicis brevis (APB), as this muscle was utilised for excitability testing.

2.1. Neurophysiological studies

In addition to clinical examination, cortical function was assessed using previously described threshold tracking transcranial magnetic stimulation (TMS) techniques (Vucic et al., 2006). Two high-power magnetic stimulators connected to a BiStim device (Magstim Co., Whitland, South West Wales, UK) produced magnetic currents and enabled conditioning and test stimuli to be independently set and administered through the one coil. These were applied over the motor cortex utilizing a 90 mm circular coil, oriented to induce current flow in a posterior-anterior direction and the resultant motor evoked potential (MEP) was recorded from APB. The optimal position for a motor evoked potential (MEP) from the right APB muscle was obtained by adjusting the coil position. The MEP was measured from peak to peak and the threshold tracking target set to 0.2 mV, the midpoint of the steepest portion of the logarithmic stimulus response curve (Fisher et al., 2002). This threshold tracking technique overcomes the marked variability in the MEP amplitude with successive stimuli related to spontaneous variations in the resting threshold of cortical neurons, as may occur with conventional constant paired test stimuli TMS techniques in which changes in the amplitude of the test response is measured (Kiers et al., 1993; Weber and Eisen, 2002). The APB muscle was at rest for the recording of all neurophysiological parameters (except the cortical silent period) and the surface EMG closely observed for the presence of voluntary activity.

Single-stimulus TMS was used to record *stimulus–response* (*SR*) curves, *resting motor threshold* (RMT), *central motor conduction time* (*CMCT*) and *cortical silent period* (*CSP*) duration. Three stimuli were delivered at each level of stimulus intensity. RMT was the stimulus intensity that maintained a target MEP of 0.2 mV, which was the middle of the steepest portion of the logarithmic stimulus response curve and the MEP was measured from peak to peak. The maximum MEP amplitude (MEP/CMAP, %) and minimum MEP onset latency (ms) was calculated from the average of three stimuli delivered at 150% RMT. CMCT (ms) was calculated according to the F-wave method (Claus, 1990). CSP was produced by a single-pulse TMS while subjects performed a weak voluntary contraction. The duration of the silent period was determined from the beginning of the MEP to the return of EMG activity.

Threshold tracking paired-pulse TMS studies were performed (Vucic et al., 2006). In the paired-pulse paradigm a subthreshold conditioning stimulus preceded a suprathreshold test stimulus at increasing interstimulus intervals (ISIs) as follows: 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 10, 15, 20, and 30 ms. Three stimulus combinations were delivered sequentially and monitored: (i) the intensity required to produce the unconditioned test response (RMT); (ii) the subthreshold conditioning stimulus alone, verifying that the subject remained relaxed and no MEP response was produced; (iii) conditioning and test stimuli in combination. When two consecutive MEP responses were within 20% of the target response (0.2 mV), tracking was deemed acceptable and the computer advanced to the next ISI. The subthreshold conditioning stimulus (70% RMT) was such that it did not evoke a response. Intracortical inhibition induced by a conditioning stimulus was measured as the increase in the test stimulus intensity required to produce the target MEP and calculated with the following formula:

$$\text{Inhibition} = (\text{Conditioned test stimulus intensity} - \text{RMT})/\text{RMT} * 100$$

Two distinct physiological phases of SICI have been recognized in healthy subjects, occurring at ISIs $\leqslant$ 1 ms and 3 ms, ascribed to axonal refractoriness and activation of different inhibitory circuits, and both are reported (Vucic et al., 2006; Fisher et al., 2002). Facilitation was measured as the decrease in the conditioned test stimulus intensity required to produce the target MEP. In normal