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Altered motor axonal excitability in patients with cervical spondylotic amyotrophy

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HIGHLIGHTS

- Motor excitability is different between cervical spondylotic amyotrophy (CSA) cases and controls.
- Evidence for a reduction in slow K^+ conductance was found in both distal- and proximal-type CSA cases.
- Abnormal excitability changes may contribute to the increased vulnerability of motor axons in CSA.

ABSTRACT

Objective: To investigate the changes in motor axonal excitability properties in cervical spondylotic amyotrophy (CSA).
Methods: Threshold tracking was used to measure the median motor axons in 21 patients with CSA, 10 patients with cervical spondylotic radiculopathy (CSR) and 16 normal controls.
Results: Compared with normal controls, patients with distal-type CSA showed increased threshold electrotonus hyperpolarization (TEh [90–100]) and increased superexcitability on the symptomatic side ($P < 0.05$), which are suggestive of distal motor axonal hyperpolarization, presumably due to motor axonal regeneration. More importantly, compared with normal controls and CSR cases, both distal- and proximal-type CSA cases showed lower accommodation during depolarising currents (reduced S2 accommodation, decreased TEd [undershoot] and/or lower subexcitability) ($P < 0.05$), indicating that slow K^+ conductance may be less active in motor axons in patients with CSA.
Conclusions: The present study demonstrated changes in motor axonal excitability in patients with CSA compared with both normal controls and patients with CSR.
Significance: Less expression of slow K^+ conductance may confer greater instability in membrane potential in CSA, thereby presumably contributing to the increased vulnerability of motor axons in patients with CSA.

1. Introduction

Cervical spondylotic amyotrophy (CSA) is a special type of cervical spondylosis that is characterised by severe weakness and amyotrophy in the upper limbs with no or insignificant sensory involvement and no lower extremity symptoms (Shinomiya et al., 1994; Sonoo, 2016). According to the distribution of muscular atrophy, CSA is classified as proximal or distal type (Jiang et al., 2011; Zheng et al., 2017).

The true pathogenesis of CSA has not been well established. One of the current hypotheses regarding the aetiology of CSA mainly involves the selective damage of ventral nerve roots and/or anterior horn cells by a bony spur or herniated disc (Keegan, 1965; Itoh et al., 1980), and the relatively good results obtained with cervical surgical treatment, especially in proximal-type CSA (Fujiwara et al., 2006; Wang et al., 2014), support this hypothesis. Although the sensory nerve action potentials (SNAPs) recorded in distal

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nerves are normal in cervical spondylosis because of preganglionic injury, most cases with cervical spondylosis have initial symptoms of upper limb radiation pain and/or sensory impairment in clinical practice because sensory fibres are more susceptible to compressive injury than motor fibres are in radiculopathy (Wilbourn and Aminoff, 1998; Alfonsi et al., 2003). Therefore, it is difficult to explain why motor fibres are peculiarly vulnerable to compression in patients with CSA.

Previous studies have demonstrated that the different excitability properties of axons may cause different responses to injury or disease (Burke et al., 2001; Kuwabara et al., 2000; Kuwabara et al., 2001; Lin et al., 2000; Lin et al., 2001). For example, there are significant differences in the properties of peroneal and median motor axons; as a result of these differences, peroneal axons have less protection from damage and are more likely to become ectopically active (Kuwabara et al., 2000; Kuwabara et al., 2001). Similar conditions were also reported between median and sural sensory axons, and the inherent differences in nerve excitability between these nerves may result in a greater tendency for dysfunction in sural afferents (Lin et al., 2000; Lin et al., 2001). In clinical practice, Han et al. demonstrated that an ischaemic insult may cause a higher intensity of numbness and paraesthesia in patients with carpal tunnel syndrome (CTS) than observed in healthy subjects because of a preexisting abnormal axon excitability in CTS (Han et al., 2009). Therefore, it may be important to identify the motor axonal excitability in patients with CSA to explore its pathogenesis. Unfortunately, no studies have reported the possibility of changes in motor axonal excitability in patients with CSA because it is not possible to directly measure human motor axon excitability in vivo.

The recently developed threshold tracking technique provides a non-invasive and painless way to explore a number of indices of axonal excitability (e.g., strength-duration properties, threshold electrotonus, superexcitability, late subexcitability and refractoriness) (Bostock et al., 1998; Burke et al., 2001). These indices shed light on both the sodium (Na^+) and potassium (K^+) channels, the properties of axon membranes, and membrane potential (Bostock et al., 1998; Burke et al., 2001). Using this nerve excitability testing, the aim of our study was to investigate the changes in axonal excitability properties in patients with CSA and analyse the correlation between the altered motor axonal excitability and increased vulnerability of motor axons in CSA.

2. Materials and methods

2.1. Subjects

Twenty-one patients with CSA (distal-type vs. proximal-type: 16 vs. 5) (Fig. 1), 16 healthy subjects and 10 patients with cervical spondylotic radiculopathy (CSR) were included in this study (Table 1). All patients were recruited at Huashan Hospital between February 2016 and September 2017. The Human Ethics Committee of Huashan Hospital at Fudan University in China granted ethical committee approval, and each subject provided informed consent.

The subjects in the control and both the CSA and CSR patient groups were selected according to the inclusion and exclusion criteria that have been described previously (Zheng et al., 2014; Zheng et al., 2017).

2.2. Testing methods

As previously described (Sawai et al., 2011; Klein et al., 2018), nerve excitability testing was performed by a protocol using a computer program (QTRAC version 4.3 with multiple excitability protocol TRONDF; Institute of Neurology, London, UK). The tests were performed on both sides of all subjects in the patient groups and five subjects in the control group, and the remaining 11 healthy subjects underwent unilateral upper limb detection. Compound muscle action potentials (CMAPs) were recorded using a belly-tendon method from the abductor pollicis brevis (APB) to median nerve stimulation at the wrist, and the CMAP amplitude was measured from the baseline to the initial negative peak.

Stimulation was delivered by an isolated linear bipolar constant current stimulator (maximal output ±50 mA) (DS5, Digitimer Ltd, Welwyn Garden City, UK) controlled by the QtracS software (© Prof. H. Bostock, Institute of Neurology, London, UK). The optimal position of the stimulation cathode was determined in each subject using a hand-held stimulator, prior to the application of surface electrodes (Disposable Silver/Silver Chloride cup electrodes, Digitimer Ltd, Welwyn Garden City, UK) secured with a strap, and the reference electrode was placed 10 cm proximal to the stimulation cathode. Skin temperature was monitored at the stimulation site, a heater was used to maintain the temperature above 32 °C, and both the stimulating and recording sites were prepared by lightly abrading the skin with fine sandpaper.

The following measures were performed using the TRONDNF protocol (Burke et al., 2001; Sawai et al., 2011; Murray and Jankelowitz, 2011): (1) stimulus-response curves (S-R curves): the stimulus was manually increased to obtain the maximal CMAP, and the curve was repeated in smaller increments of stimulus by the computer. The current that chouls produce 40% of the maximal CMAP amplitude was defined as the "threshold". (2) Strength-duration time constant (SDTC): the SDTC for median motor axons was measured using five different stimulus durations (0.2–1.0 ms) to determine the altered stimulus current required to reach the "threshold". Weiss's formula [$SDTC = 0.2 \times (I_{0.2} - I_{1.0})/(I_{1.0} - 0.2 \times I_{0.2})$] was used to measure the STDC. (3) Threshold electrotonus (TE): TE was tested using subthreshold 100-ms polarising currents in the depolarising (TEd; +40%) and hyperpolarising (The; −40%) directions. The threshold change (%) was plotted with the depolarising and hyperpolarising directions at various time intervals. (4) Recovery cycle: the recovery cycle of axonal excitability after a single supramaximal stimulus was recorded by delivering the test stimulus at different intervals (from 2 to 200 ms) after the conditioning stimulus. (5) Current-threshold relationship: the current-threshold (I/V) relationship is analogous to the current-voltage relationship. The threshold was measured 200 ms after the onset of a polarising current lasting 200 ms. The polarising conditioning current was ramped up from +50% of the control threshold to −100% in the 10% step.

Furthermore, all subjects in this study underwent further cervical MRI evaluation, bilateral handgrip strength (HGS) examination (Jamar hydraulic hand dynamometer, Sammons Preston Rolyan, IL, USA) and bilateral electrophysiological detection (Nihon Kohden MEB-9400, Japan), including the sensory and motor conduction of the median, ulnar, peroneal and tibial nerves, and concentric needle electromyogram (EMG) examination. These parameters for each patient were defined as abnormal if the measurements were 2 standard deviations (SDs) above the average values for normal controls for the onset-latency or 2 SDs below the average values for normal controls for the maximal amplitude, nerve conduction velocity and HGS.

2.3. Statistical methods

All data were analysed using SPSS version 12.0 (IBM, USA). The Kolmogorov-Smirnov test was used to test normally distributed data. The measurements in patients with distal- or proximal-type CSA, the cases with CSR and the healthy subjects were compared by one-way ANOVA (Bonferroni correction), and independent t-tests were used to evaluate the differences in the excitability