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Motor unit remodelling in multifocal motor neuropathy: The importance of axonal loss

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HIGHLIGHTS

- Axonal degeneration is an integral part of the disease process in MMN.
- Axonal loss in MMN may be masked by prominent re-innervation.
- Nerve conduction studies are not sensitive to motor unit remodelling in MMN.

ABSTRACT

Objective: To estimate the degree of axonal loss in patients diagnosed with multifocal motor neuropathy (MMN) using a novel assessment of motor unit numbers and size.
Methods: Automated motor unit number estimation using a compound muscle action potential (CMAP) scan was undertaken in median nerves with conduction block. Results were compared with 30 age-matched healthy controls.
Results: Compared with healthy controls, MMN patients had fewer motor units (MMN: 33 ± 11 vs HC: 93 ± 36 [mean ± SD]; $p < 0.0001$) and larger 'size of the largest unit' (MMN: 1.2 ± 0.5 mV vs HC: 0.4 ± 0.1 mV; $p < 0.0001$), despite having normal distal CMAP amplitudes (MMN: 7.6 ± 1.8 mV vs HC: 8.7 ± 2.5 mV; $p = 0.24$).
Conclusions: MMN is associated with marked axonal loss which may be masked by striking re-innervation resulting in preservation of distal CMAP amplitudes.
Significance: Assessment of motor unit properties should be incorporated into assessment of disease progression in MMN, given that nerve conduction studies are insensitive to motor unit remodelling.

1. Introduction

Progressive axonal degeneration is a prominent feature of multifocal motor neuropathy (MMN), differentiating it from the other immune-mediated neuropathies (Vlam et al., 2011). The aim of immunomodulatory treatment with intravenous immunoglobulin (IVIg) has been to reduce the rate of axonal loss as this is the most important determinant of permanent weakness and disability (Van Asseldonk et al., 2006; Vucic et al., 2004). It has been suggested that the effectiveness of IVIg may decline over time, correlating

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with the development of axonal degeneration (Terenghi et al., 2004).

Unfortunately, mechanisms of conduction block and axonal degeneration in MMN remain poorly understood and there remains debate as to whether MMN is primarily a demyelinating or axonal disorder (Kiernan et al., 2002). Anti-GM_1 IgM is present in approximately 50% of patients with MMN with GM_1 enriched in the nodal and paranodal regions (Vlam et al., 2011; Willison and Yuki, 2002). It has recently been suggested that disease processes targeting these regions represent a distinct group of neuropathies characterised by a continuum from conduction block to axonal degeneration, a concept which may be pivotal in understanding the pathophysiology of conditions such as MMN (Uncini and Kuwabara, 2015).

Axonal loss is typically only identified late in the disease process and only once the compound muscle action potential (CMAP) amplitude has reduced on nerve conduction studies (NCS). The present study was prompted by the frustration at the lack of an objective method to monitor treatment response and disease progression in MMN patients. As such, a novel technique was utilised to quantify the degree of axonal loss and compensatory reinnervation in MMN as a potential tool for disease monitoring.

2. Methods

2.1. Patient cohort and selection criteria

Consecutive patients fulfilling European Federation of Neurological Societies/Peripheral Nerve Society criteria for MMN (definite or probable) were prospectively recruited between April 2015 and December 2016. Cases of 'possible' MMN were excluded (Joint Task Force of the EFNS and the PNS, 2010). Results were compared with 30 healthy control subjects who were screened based on their medical history. All participants gave written informed consent to participate in the study. The study was approved by the Sydney Local Health District Ethics Review Committee (Royal Prince Alfred Hospital).

2.2. Assessment tools

Muscle strength was assessed using Medical Research Council (MRC) grading by a single investigator (N.G.) in 15 muscle groups bilaterally (shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension, finger extension, finger flexion, first dorsal interosseus, abductor digiti minimi, thumb abduction, hip flexion, knee flexion, knee extension, ankle dorsiflexion and ankle plantarflexion). The MRC grades were summed to calculate an expanded MRC sum-score (maximum score 150). Serum from each patient was tested for anti-GM1 IgM antibodies as previously described (Yuki et al., 1997).

2.3. Nerve conduction studies

All patients underwent NCS at the time of recruitment by a single neurologist/neurophysiologist (N.G.) to ensure criteria for MMN were fulfilled and to identify median nerves with conduction block within the forearm segment. All patients had motor NCS of the median nerves bilaterally with stimulation at the wrist and elbow and recording over abductor pollicis brevis. In addition, patients underwent ulnar, common peroneal and tibial motor studies and median, ulnar and radial sensory studies unilaterally. Conduction block was defined as negative peak CMAP area reduction of at least 30% on stimulation of wrist versus elbow with duration increase of 30% or less, or CMAP area reduction of 50% when CMAP duration increase was greater than 30% (Joint Task Force of the EFNS and the PNS, 2010).

2.4. Assessment of motor unit properties using a novel CMAP scan

CMAP scans (Bostock, 2016) were recorded using the TRONDNF protocol within QTRACW software (© Institute of Neurology, University College London, UK). All recordings were undertaken by stimulating the median nerve at the wrist with a 0.2 ms wide stimulus using an isolated constant current stimulator (DS5; Digitimer, Welwyn Garden City, UK). The active recording electrode was placed over the motor point of abductor pollicis brevis and reference electrode over the proximal phalanx. The stimulus strength was manually increased until the supramaximal CMAP was reached. Following this, stimuli were delivered twice per second with each stimulus intensity being 99.8% of the preceding stimulus until no response was recordable. 20 pre- and post-scan sweeps were recorded to assess variability of supramaximal (*MScan Peak*) and baseline responses respectively with each scan taking approximately 5 min in total.

The *MScanFit* program contained within the *QTRACW* software was used to derive a motor unit number estimate (*MUNE*), and *Size of the largest unit* (in *mV* and as a percentage of the *MScan Peak*). The program uses a mathematical model to simulate the recorded scan. The modelled scan is then 'fitted' to the recorded scan by making sequential adjustments until the discrepancy between the two scans is minimised as previously described (Bostock, 2016).

Median nerves with forearm conduction block were selected for the current study as this is a frequent site of involvement in typical MMN and the forearm segment is not a typical site of entrapment neuropathy. Median nerves with distal motor latency prolongation on NCS (>4 ms) were excluded due to the possibility of entrapment neuropathy at the wrist. In patients with bilateral median nerve forearm CB, only results from one side were used in the analysis.

2.5. Statistics

An independent samples t-test was used to compare age, *MScan Peak* and *MUNE* between MMN patients and healthy controls. Results of the *Size of the largest unit* were not normally distributed in MMN patients. Hence, the Mann-Whitney U test was used. Pearson correlation coefficient was used to investigate the relationship between *MUNE*, *MScan Peak* and age followed by linear regression analysis. Significance was defined by a p-value of <0.05. Results are presented as mean ± standard deviation. Statistical analysis and graph construction was performed using Graph Pad Prism 7 and IBM SPSS Statistics (Version 22).

3. Results

A total of 12 patients fulfilling EFNS/PNS criteria for definite or probable MMN were recruited. All MMN patients were established and controlled on maintenance IVIg therapy. Ten patients were identified with median nerve motor conduction block in the forearm. Two patients had high thresholds limiting supramaximal stimulation and hence accurate motor unit number estimation could not be calculated. The remaining eight patients underwent median nerve CMAP scans on the ipsilateral side of conduction block. Clinical and laboratory features of the patients were typical of MMN (Table 1). Results were compared with recordings from 30 healthy controls [13:17 (M:F)] who were of similar age (MMN: 54.6 ± 13.6; HC: 55.1 ± 16.5; p = ns). 63% of MMN patients were