Clinical Neurophysiology 128 (2017) 235–240

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Monitoring the short-term effect of intravenous immunoglobulins in multifocal motor neuropathy using motor unit number index

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ARTICLE INFO

Article history:
Accepted 12 November 2016
Available online 01 December 2016

Keywords:
Multifocal motor neuropathy
Motor unit number index
Dysimmune neuropathy
Intravenous immunoglobulins

HIGHLIGHTS

- MUNIX was used to test therapeutic response to intravenous immunoglobulins (IVIg) in multifocal motor neuropathy (MMN) patients.
- MUNIX sum-score was lower in MMN patients than in healthy controls.
- MUNIX sum-score improved quickly after intravenous immunoglobulin treatment in MMN.

ABSTRACT

Objective: To determine whether motor unit number index (MUNIX) is pertinent to monitor the effect of intravenous immunoglobulins (IVIg) in multifocal motor neuropathy (MMN).
Methods: MUNIX was assessed longitudinally in 7 MMN patients and 17 healthy controls in the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles. A MUNIX sum-score and a compound muscle action potential (CMAP) sum-score were calculated by summing up the scores of APB and ADM. MMN patients were evaluated on the first day of IVIg infusion, 5 MMN patients were evaluated 22 days after IVIg infusion, and 3 MMN patients were evaluated 1 month after two IVIg infusions.
Results: Intraclass correlation coefficient of the MUNIX sum-score in healthy controls was 0.85, showing good test–retest reproducibility. MUNIX and CMAP sum-scores were lower in MMN patients than in healthy controls ($p < 0.01$ and 0.02, respectively). MUNIX sum-score improved in three of the five patients 22 days after IVIg infusion and in two of the three patients 1 month after 2 IVIg infusions, whereas CMAP sum-score improved in only one patient in both evaluations.
Conclusions: In this preliminary study, MUNIX seems to be a reliable and sensitive tool to monitor the short-term efficiency of IVIg in MMN.
Significance: MUNIX can help monitor IVIg treatment in MMN.

1. Introduction

Multifocal motor neuropathy (MMN) is an immune-mediated, purely motor neuropathy, characterized by an asymmetrical, progressive, and primarily distal muscle weakness, which generally starts and predominates in the upper limbs (Nobile-Orazio et al., 2005; Léger et al., 2015). Electrophysiological studies show persistent multifocal conduction blocks on motor nerves, with normal sensory nerve conduction study. First-line treatment is intravenous immunoglobulins (IVIg), with a success rate of approximately 80% (Azulay et al., 1994; Van den Berg et al., 1995; Federico et al., 2000; Léger et al., 2001; Hahn et al., 2013). Most patients need repeated IVIg infusions for a long term. Maintenance IVIg therapy should be tailored based on the clinical response of the patients (Berg-Vos et al., 2002; Slee et al., 2007). Nevertheless, clinical assessment may not be sensitive enough to monitor the response to IVIg; therefore, clinicians need more sensitive markers to measure disease progression.

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http://dx.doi.org/10.1016/j.clinph.2016.11.012
1388-2457/

Electromyography is mandatory to diagnose MMN and is considered as quantitative data; however, it is uncommonly applied as outcome measures in the monitoring of MMN patients. Motor unit number index (MUNIX) (Nandedkar et al., 2004, 2010) is a new electrophysiological technique that estimates the number of functional motor units for each analyzed muscle. MUNIX has the advantage over the currently available motor unit number estimation techniques of being a rapid and easy-to-perform method which only requires measurable compound muscle action potentials (CMAP). MUNIX was reported to be useful in measuring motor unit loss in patients with amyotrophic lateral sclerosis (Nandedkar et al., 2010; Boekestein et al., 2012; Furtula et al., 2013; Neuwirth et al., 2015) and axonal loss in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Paramanathan et al., 2016). MUNIX demonstrated proper reproducibility in ALS and healthy controls (Ahn et al., 2010; Nandedkar et al., 2011; Neuwirth et al., 2011, 2016; Fathi et al., 2016). We have recently demonstrated that MUNIX has a good reproducibility and is related to the disability in CIDP (Delmont et al., 2016).

In this study, we assessed whether MUNIX was modified after IVIg treatment in MMN patients. Our aim was to determine if MUNIX was relevant to monitor the response to treatment in MMN.

2. Methods

2.1. Subjects

Seven MMN patients fulfilling the Joint Task Force of the EFNS and the PNS 2010 criteria (Joint Task Force of the EFNS and the PNS, 2010) were enrolled at the Department of Neuromuscular Disorders in the University Hospital of Marseille, France, between February and August 2015. All patients presented MMN with conduction blocks evidenced by nerve conduction studies. Clinical and electrophysiological characteristics of the MMN patients are summarized in Table 1. Seventeen healthy controls were included. All patients and controls gave informed consent prior to the study enrolment.

2.2. Clinical assessment

Clinical assessment was performed by the same trained rater at every visit. Disability was evaluated by overall neuropathy limitation scale (ONLS) (Graham and Hughes, 2006). Muscle strength was measured by the Medical Research Council (MRC) scale in the two muscles of interest: abductor pollicis brevis (APB) and abductor digiti minimi (ADM). MRC sum-score was calculated by summing up the APB and ADM scores.

2.3. MUNIX procedure

MUNIX was performed on APB and ADM muscles for all patients and controls. Studies were performed on the most affected side for each patient.

Records were made using commercially available Keypoint machine (Medtronic, Copenhagen, Denmark), disposable pregelled surface 10-mm^2 electrodes, and handheld bipolar stimulator with saline-soaked electrodes. Subjects were positioned in a comfortable supine position during measurements. The bandpass filter setting was 3–3000 Hz. Skin temperature was >32 °C. Points of stimulation, placement of recording electrodes, and distances between active and reference electrodes were standardized as described in the original technique (Nandedkar et al., 2004; Neuwirth et al., 2010). Flat baseline was controlled before the examination. The first step consisted of recording the CMAP amplitude by supramaximal stimulation. The position of the active recording electrode was adjusted so as to achieve the highest possible CMAP amplitude (van Dijk et al., 1995; Bromberg and Spiegelberg, 1997) to optimize the reliability of the technique (Ahn et al., 2010; Nandedkar et al., 2010; Neuwirth et al., 2010; Sandberg et al., 2011). The size of the negative phase was used to calculate the CMAP amplitude. Then, the surface electromyography interference pattern (SIP) was recorded with a time analysis of 300 ms epochs, 10 times for each muscle, at five different force levels. The patient was asked to give a voluntary contraction against the resistance provided by the operator at increasing isometric force levels (10%, 25%, 50%, 75%, and then 100% of the maximal force) with 15 s of rest between 75% and 100% and 30 s between the two series. Maximum contraction was performed initially as a reference for the patient to estimate his/her strength. SIP area, SIP power, and ideal case motor unit count (ICMUC) were calculated for each SIP recording.

The criteria to accept SIP epochs, previously described, to avoid interference with volume-conducted activity of neighboring muscles that could influence MUNIX calculation, were SIP area >20 mVms, ICMUC <100, SIP area/CMAP area >1 (Nandedkar et al., 2010) and CMAP >0.5 mV.

Finally, electromyography measures were used to calculate MUNIX and motor unit size index (MUSIX) by means of an Excel file. Ten valid ICMUC-SIP area combinations were required for a reliable regression analysis for MUNIX computation. MUNIX tests lasted approximately 15 min.

We added the MUNIX, MUSIX and CMAP amplitude scores of the APB and ADM muscles to compute MUNIX sum-score, MUSIX sum-score, and CMAP sum-score.

2.4. Study design

Patients were examined at two different time points. Five patients were evaluated on the first day of IVIg infusion (day 1), considered as the worst clinical state, and 22 days after the infusion (day 22) (interquartile range 20–23) corresponding to the beginning of the third week after the end of the infusion. The action of IVIg lasts at least 3 weeks after the infusion (half-life of IgG is 21 days). Hence, in the recommendations of EFNS PNS the interval of IVIg infusion is every 2–4 weeks (EFNS 2010 MMN). We therefore used the comparison between days 1 and 22 to evaluate the short-term efficiency of IVIg infusion. Three recently diagnosed patients received their first IVIg infusion during the inclusion period and were investigated on the first day of the first infusion (Infusion 1) and also on the first day of the third infusion (Infusion 3). The median interval between two infusions was 6 weeks. The comparison between Infusion 1 and Infusion 3 was used to evaluate the response to treatment at a longer term. All patients were treated with the same dose of IVIg of 2 g/kg. All the evaluations included a clinical and an electrophysiological examination that were performed by the same investigator trained for this technique, with the same electrode placement.

MUNIX was assessed twice in 17 healthy controls, with a median interval of 10 days (7–14 days).

2.5. Statistical analysis

The intra rater variability of MUNIX in the control group was determined with an intraclass correlation coefficient (ICC). The best reproducibility is achieved if ICC is equal to 1. In previous studies MUNIX reproducibility was considered good if ICC >0.75 (Futurla et al., 2013). To assess normative data, we calculated the coefficient of variation (COV) between the two measures of MUNIX sum-score, MUSIX sum-score, and CMAP sum-score in the control group. COV was calculated as the absolute difference between test