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Predictive values of motor unit potential analysis in limb muscles ☆

Simon Podnar *

Institute of Clinical Neurophysiology, Division of Neurology, University Medical Center Ljubljana, SI-1525 Ljubljana, Slovenia

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ABSTRACT

Objective: In interpretation of diagnostic findings the probability that an abnormal test accurately indicates pathology (i.e., the positive predictive value), and a normal test accurately excludes pathology (i.e., the negative predictive value) is the most important. For motor unit potential (MUP) analysis no such data has been published; hence this was the aim of this study.
Methods: In 31 patients with facioscapulohumeral muscular dystrophy (FSHD) and 34 controls the biceps brachii and vastus lateralis muscles were examined by concentric needle electromyography (EMG), using template operated MUP analysis. These results were compared to non-parametric reference data obtained in another group of 34 (biceps brachii) and 46 (vastus lateralis) control subjects.
Results: For the biceps brachii muscles sensitivity was 59%, specificity 91%, the positive predictive value 85%, and negative predictive value 72% with at least two criteria (mean values or outliers for MUP thickness, amplitude and duration) below the reference intervals. In addition, all subjects with three abnormal EMG criteria were FSHD patients, and 90% of subjects with normal EMG were controls.
Conclusions: Template operated MUP analysis demonstrated reasonable predictive value for diagnosis and exclusion of myopathy.
Significance: Quantitative MUP analysis seems to be useful for the preliminary diagnosis of FSHD in patients with appropriate clinical picture.

1. Introduction

For a clinician interpreting the findings of a diagnostic test the most important information is the predictive values of the test, i.e., the probability that an abnormal test accurately indicates pathology (positive predictive value), and that a normal test accurately excludes pathology (negative predictive value) (Altman, 1991). Although there is some data on the sensitivity (Barkhaus et al., 1990; Buchthal and Kamieniecka, 1982; Nirkko et al., 1995; Podnar and Zidar, 2006; Stewart et al., 1989) and specificity (Libelius and Johansson, 2000; Nirkko et al., 1995; Podnar, 2004; Stalberg et al., 1994; Tison et al., 2000) of motor unit potential (MUP) analysis, there is no data on the predictive value of quantitative electromyography (EMG).

In this study, quantitative MUP analysis was performed in a group of controls and in a group of patients with a molecular-genetic diagnosis of facioscapulohumeral muscular dystrophy (FSHD) (Podnar and Zidar, 2006). Multi-MUP analysis was performed in two typical limb muscles (i.e., biceps brachii and vastus lateralis). From the data obtained, the sensitivity, specificity, the positive and negative predictive values, and likelihood ratios of the test were calculated.

2. Methods

The control group was composed mainly of healthy volunteers partially included in our previous study (Martic and Podnar, 2008), with the addition of several subjects with subjective complaints of generalized weakness. These subjects showed normal muscle bulk and strength on clinical examination, and normal serum creatine kinase (CK) activity on laboratory testing (Podnar, 2008). The patient group consisted of symptomatic subjects from our register of neuromuscular disorders or diagnosed clinically during time of our previous study (Podnar and Zidar, 2006) with a genetic diagnosis of FSHD. The study was approved by the National Ethics Committee of Slovenia, and all subjects provided informed consent.

Quantitative MUP analysis of the biceps brachii and vastus lateralis muscles was performed using a standard concentric EMG needle, and a commercially available EMG system (Keypoint, Alpine Biomed Neurodiagnostics, Skovlunde, Denmark) with standard settings (filters: 5 Hz–10 kHz). Right-sided muscles were examined in all subjects. At slight voluntary activation when EMG system usually sampled 3–5 MUPs on each muscle position (Podnar and

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* Tel.: +386 1 522 1500; fax: +386 1 522 1533.
E-mail address: simon.podnar@kclj.si.

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Vodusek, 1999), we attempted to obtain at least 20 different MUPs from each muscle using template operated multi-MUP analysis. The validation of this technique was previously described (Stalberg et al., 1995). MUPs were carefully reviewed, and those with obvious errors in duration cursors positioning were deleted. However, duration cursors were not changed. MUP amplitude, duration, area, number of phases, number of turns, and spike duration were measured. In addition, MUP thickness (Nandedkar et al., 1988) and size index (Sonoo and Stalberg, 1993) were calculated. Only muscles with at least 20 MUPs sampled were included in further analyses.

MUP parameters from controls' and patients' muscles were compared to the non-parametric confidence intervals for mean values (lower limit: 5th percentile, upper limit: 95th percentile), and to the "outlier" confidence intervals (lower limit: 5th percentile of the 3rd/20 MUPs, upper limit: 95th percentile of the 18th/20 MUPs) (Podnar, 2005, 2008; Stalberg et al., 1994). Confidence intervals were obtained from a control population (biceps brachii: 34; vastus lateralis: 46 subjects) included in an international multi-centric compilation of reference MUP data, which has been previously published (Bischoff et al., 1994). To declare the muscle abnormal for an individual MUP parameter, the mean value or at least 3 (out of 20) individual MUPs (outliers) had to be outside of the reference range (Stalberg et al., 1994). Changes were designated "myopathic" if MUP parameter values (except number of phases and number of turns) were below the reference range.

The prevalence (%) of FSHD in authors' EMG practice was calculated from the population of patients with clinically suspected FSHD consecutively referred to the author in the period 2004–2008 for quantitative MUP analysis as [number of patients with positive FSHD genetic test/number of evaluated patients with suspected FSHD $\times$ 100)]. During genetic testing, DNA digestion with EcoR-I and Bln-I restriction enzymes was followed by Southern Blot analysis using the genomic hybridization probe p13E11 (Wijmenga et al., 1992). The diagnosis of FSHD was confirmed by detection of short fragments ($< 35\ kb$) within the FSHD-locus on chromosome 4q35 (Tupler and Gabellini, 2004).

The specificity of the MUP analysis was then calculated for individual MUP parameters, separately for mean values and for outliers, and also when both applied concomitantly (combined) (Sensitivity for individual MUP parameters in the same patient population has been previously published (Podnar and Zidar, 2006)). Furthermore, the sensitivity, specificity, positive predictive value, negative predictive value, pre-test odds, the likelihood ratio, and post-test odds were calculated for the following combinations of MUP parameters: (A) MUP area, duration and number of turns ("neuropathy set") (Podnar and Mrkaic, 2002); (B) MUP thickness, duration, and number of phases ("standard myopathy set"); (C) MUP thickness, amplitude, and duration (biceps brachii), and area (vastus lateralis) ("empirical myopathy set") (Podnar and Zidar, 2006); (D) all eight MUP parameters. Indices of diagnostic performance were calculated when at least 1, at least 2, and at least 3 diagnostic criteria (MUP parameters' mean values and outliers) were below (above for number of phases and turns) the appropriate reference range (Podnar, 2004). The sensitivity (%) of testing was calculated as [number of patients with abnormal test/number of evaluated patients $\times$ 100)]; specificity (%) as [number of controls with normal test/number of evaluated controls $\times$ 100)]; the positive predictive value (%) as [number of patients with abnormal test/number of evaluated patients and controls with abnormal test $\times$ 100)]; the negative predictive value (%) as [number of controls with normal test/number of evaluated controls and patients with normal test $\times$ 100)]; pre-test odds as [prevalence/1-prevalence], the likelihood ratio as [sensitivity/(1-specificity], and post-test odds as [pre-test odds $\times$ likelihood ratio] (Altman, 1991).

3. Results

Quantitative MUP analysis was performed in 34 control subjects (18 men), aged 24–81 (median, 40) years (calculation of specificity), and in 31 patients (17 men), aged 22–77 (median, 43) years (calculation of sensitivity) (Podnar, 2008; Podnar and Zidar, 2006). Adequate MUP samples were obtained in all tested control muscles; 34 for the biceps brachii and 31 for the vastus lateralis. By contrast, in two patients with the most severe disease muscles (biceps brachii and vastus lateralis in one, only biceps brachii in another) were atrophied to such extent that adequate sampling was not possible. Therefore, at least 20 MUPs were sampled in 29 biceps brachii and in 30 vastus lateralis muscles of 31 FSHD patients (Podnar and Zidar, 2006). Prevalence of FSHD in population included in this study was therefore 48% [31/(31 + 34) $\times$ 100%], and 50% [31/(31 + 31) $\times$ 100%], and the pre-test odds 0.92 [48%/52%], and 1.00 [50%/50%] for biceps brachii and vastus lateralis muscles, respectively.

In the period 2004–2008 the author performed quantitative MUP analysis in 111 patients with suspected myopathy. In 15 of these patients FSHD was suspected. Diagnosis was genetically confirmed in eight patients. Of remaining seven patients muscular dystrophy was diagnosed in 2, other unspecified myopathy in 2, and no definite neuromuscular disorder in 3. The prevalence of FSHD patients in the author's quantitative EMG practice was therefore 53% [8/15 $\times$ 100%], and the pre-test odds was 1.13 [53%/47%].

Specificities of MUP analysis for individual MUP parameters were, in general, above 80%. They were higher for mean values than for outliers, higher for the vastus lateralis than for the biceps brachii, and in vastus lateralis higher for values > 95 percentiles (neuropathic, except for number of phases and number of turns) than for values < 5 percentiles (myopathic, except for number of phases and number of turns) (Table 1).

Table 2 shows the sensitivity, specificity, positive predictive value, negative predictive value, and the likelihood ratio for four combinations of MUP parameters, and for 1–3 diagnostic criteria required to be below (above for number of phases and turns) the appropriate reference range (Podnar, 2004) to diagnose myopathy in the biceps brachii and vastus lateralis muscles. In general, specificity and positive predictive value were somewhat higher than sensitivity and negative predictive value. Combination of MUP thickness, amplitude and duration (biceps brachii) or area (vastus lateralis) demonstrated the highest values of diagnostic indices, which were in general higher in biceps brachii than in vastus lateralis muscle (Table 2).

4. Discussion

Although our previous study demonstrated myopathic quantitative MUP changes in 77% of FSHD patients' biceps brachii muscles with normal, and in 100% with weak elbow flexion (Podnar and Zidar, 2006), the test sensitivity does not provide much information about the meaning of a pathologic or normal test in an individual patient. This information is provided by the positive and negative predictive values or the likelihood ratio and post-test odds of the test, which were calculated in this study.

The main result of this study was that, using identical diagnostic criteria to those in our previous study (Podnar and Zidar, 2006), all patients with an abnormality in the biceps brachii muscle in at least 3 out of 6 diagnostic criteria had FSHD (i.e., positive predictive value, 100%, Table 2). Using quantitative MUP analysis a definite diagnosis of myopathy was possible in 41% of FSHD patients (i.e., sensitivity) from a group with normal elbow flexion strength (5/5 according to the MRC scale) (Guarantors of the Brain, 2000) in 45% of patients. In patients with MUP analysis abnormal to such