Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Original research article

Motor unit reorganization in progressive muscular dystrophies and congenital myopathies

Elżbieta Szmidt-Sałkowska, Małgorzata Gaweł, Marta Lipowska*

Department of Neurology, Medical University of Warsaw, Warsaw, Poland

ARTICLE INFO

Article history:
Received 19 May 2014
Accepted 22 May 2015
Available online 6 June 2015

Keywords:
Electromyography
Progressive muscular dystrophy
Congenital myopathy

ABSTRACT

The aim of this study was to analyze motor unit reorganization in different types of progressive muscular dystrophies and congenital myopathies.

The study population consisted of patients with genetically verified progressive muscular dystrophies: Duchenne (DMD) ($n = 54$), Becker (BMD) ($n = 30$), facio-scapulo-humeral (FSHD) ($n = 37$), and Emery–Dreifuss (E-DD) ($n = 26$). Patients with probable limb-girdle dystrophy (L-GD) ($n = 58$) and congenital myopathies ($n = 35$) were also included in the study. Quantitative EMG recordings were obtained from 469 muscles. Muscle activity at rest and during slight voluntary and maximal muscle contraction was analyzed. The motor unit activity potential (MUAP) duration, amplitude, area, size index (SI), polyphasicity, and the presence of "outliers" were evaluated.

Diminished values of MUAP parameters and decreased maximal amplitude of maximal muscle contraction were recorded most frequently in DMD and mainly in the biceps brachii muscles. SI was the most frequently changed EMG parameter. "Outliers" with amplitude below the normal range were recorded more frequently then a decreased mean MUAP amplitude (what could indicate a very high sensitivity of this EMG parameter). Pathological interference pattern was recorded in 34.7% of biceps brachii and in 21.2% of rectus femoris muscles. In FSHD, decreased MUAP duration and SI and pathological interference pattern with low amplitude were recorded most frequently in the tibial anterior and deltoid muscles.

The presence of potentials with reduced parameters is a result of decreasing motor unit area (reduced number and size of muscle fibers), while high amplitude potentials recorded in BMD and E-DD could indicate a slow and mild course of disease and muscle regeneration.

1. Introduction

1.1. *Progressive muscular dystrophies*

Progressive muscular dystrophies (PMD) are a group of congenital muscle disorders with different clinical symptoms, course, and prognosis. Some forms of PMD are associated with defects in structural proteins connected to the sarcolemma (dystrophin, various sarcoglycans, dysferin, merosin) or are directly associated with abnormalities of nuclear membrane proteins (emerin, lamin A/C). Common features of protein defects in PMD and congenital myopathies (CM) result in

* *Corresponding author at*: Department of Neurology, Medical University of Warsaw, Banacha 1A, 02-097 Warsaw, Poland. Tel.: +48 22 5992857; fax: +48 22 5991857.
E-mail addresses: ela.szmidt@wp.pl (E. Szmidt-Sałkowska), mgawel@wum.edu.pl (M. Gawel), mlipowska@wum.edu.pl (M. Lipowska).
http://dx.doi.org/10.1016/j.pjnns.2015.05.005

muscle weakness and wasting, although some differences in their phenotypes are also observed [1–9].

1.2. *Diagnosis of progressive muscular dystrophies*

Genetic testing is considered the only reliable diagnostic criterion in neuromuscular disorders but this method is rarely the first line of laboratory tests and needs guidance from other methods. Electrophysiological tests could be the first key tool for the diagnosis of primary muscle diseases, especially in limb-girdle dystrophy, and they remain very important in the evaluation of disease progression and muscle dysfunction [10–13].

1.3. *Electromyography in progressive muscular dystrophies*

By EMG, the criteria for myopathy in primary muscle diseases are most commonly fulfilled as decreased values of single motor unit action potentials (MUAPs), an increased percentage of polyphasic potentials, and a pathological interference pattern at maximal muscle activation [14–21]. In addition to short and low MUAPs, characteristic for myopathy, potentials with an increased amplitude and prolonged duration are also observed and their origin has not been sufficiently explained yet. Contribution of a neurogenic factor to reorganization of a myopathic motor unit has been discussed in the literature [16,22–25].

1.4. *Aims of the study*

The aims of the study were:

- to analyze EMG recordings obtained in progressive muscular dystrophies (PMD), including Duchenne (DMD), Becker (BMD), limb-girdle (L-GD), facio-scapulo-humeral (FSHD), and Emery–Dreifuss (E-DD) types, and in congenital myopathies (CM);
- to compare EMG data in two dystrophinopathies, quickly progressing DMD and a more benign, slowly progressing BMD;
- to compare EMG data in a dystrophinopathy (BMD) and in a nucleopathy (E-DD), both with a slow course of disease and different localization of muscle structural lesions.

2. Material and methods

2.1. *Characteristics of patients*

Two hundred and forty patients (186 M; 54 F, mean age 17.5 years) were recruited to the study at the Department of Neurology, Medical University of Warsaw, and a written informed consent was provided by all participants.

The study population consisted of genetically verified patients with four progressive muscular dystrophies: DMD, BMD, FSHD, and E-DD. In addition, patients with probable L-GD and with CM after combining clinical status data and biopsy findings were included in the study group (Table 1).

2.2. *EMG studies*

Electromyographic (EMG) recordings were obtained from 469 muscles (186 biceps brachii (BB), 219 rectus femoris (RF), and additionally in the FSHD group also 34 tibial anterior (TA), and 30 deltoid (DD) muscles) (Table 1).

Strength of the examined muscles was assessed using the MRC scale (0–5, with 0 indicating no action, and 5 indicating normal muscle strength), and muscle atrophy was assessed using a 0–3 scale (0 – no atrophy, 3 – marked atrophy).

Muscle activity was recorded during routine EMG examinations using a concentric needle electrode (DCN37 type) with 0.07 mm^2 uptake area, 0.46 mm diameter and 37 mm length. The Keypoint system (Medtronic) was used to evaluate EMG recordings. EMG recordings were registered at muscle rest and during slight voluntary (according to the multi-MUAP method) and maximal muscle contractions.

At rest, spontaneous activity was analyzed, including pseudomyotonic discharges, positive sharp waves, and fibrillations.

During voluntary muscle contraction (10–20% of maximal muscle contraction), automatic quantitative evaluation of single motor unit potentials (MUAPs) was performed, and the evaluated parameters included duration, amplitude, area, size index (SI), and polyphasicity [26–28]. The mean values of these parameters and the number of outliers (minimum 3 single MUAPs) out of the normal range were calculated [29]. Mean results were compared to the reference values according to Bischoff and Stålberg [30,31] used in our laboratory. The mean

Table 1 – Characteristics of patients.

Diagnosis	Sex		Age years (range)	Number of muscles			
	M	F		Biceps brachii	Rectus femoris	Deltoid	Tibial anterior
Duchenne muscular dystrophy	54		6 ± 2 (4–15)	27	29		
Becker muscular dystrophy	30		13 ± 6 (3–24)	35	53		
Fascio-scapulo-humeral dystrophy	23	14	28 ± 16	35	37	34	30
Emmery–Dreifuss dystrophy	26		18 ± 6	21	23		
Limb-girdle dystrophy	31	27	19 ± 11 (12–57)	42	55		
Congenital myopathies	22	13	14 ± 11	26	22		
Overall	186	54	17.5	186	219	34	30

MUAP duration was analyzed as the mean duration of all recorded MUAPs.

At maximal effort, amplitude was measured and the density of the interference pattern was estimated using visual assessment.

In addition to molecular tests muscle biopsies were performed in most of the patients with PMD (and in all patients with E-DD and CM).

2.3. *Statistical methods*

EMG results were analyzed using the following statistical methods: Student *t*-test, Wilcoxon, Shapiro–Wilk, Duncan, Kruskal–Wallis and Fisher tests, and the GLIMMIX procedure (logistic regression model). Analyses were performed using the SAS software, version 9.2. Statistical significance was set at $P < 0.05$ [32,33].

3. Results

Evaluation of conduction velocity parameters in the peripheral nerves of upper and lower limbs did not reveal any abnormalities in the whole group of patients except for one FSHD case in whom carpal tunnel syndrome was diagnosed.

In the whole examined group, typical myopathic recordings such as reduced values of MUAP parameters values and a pathological interference pattern were recorded more frequently in BB comparing to RF muscles (outliers with a decreased amplitude were recorded in 61.9% of BB and in 25.9% of RF muscles).

A reduced mean SI value was recorded in more than 50% of BB and RF muscles, most frequently in the E-DD group (in 88.9% of RF muscles) (Fig. 1).

A reduced mean SI value in both BB and RF muscles in the same patient was noted in 33.6% of cases; most frequently in the DMD group (in 55% of patients). An increased mean SI value was recorded in 5% of all examined muscles.

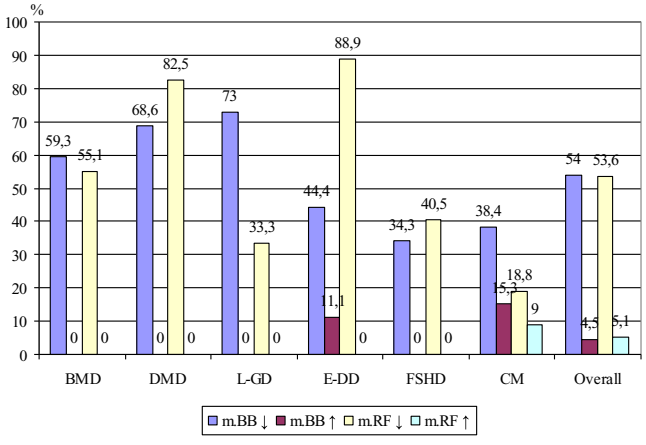

Fig. 1 – Abnormal mean MUAP size index (SI) values in PMD and CM (% of muscles).
↓ – SI below the normal range.
↑ – SI above the normal range.

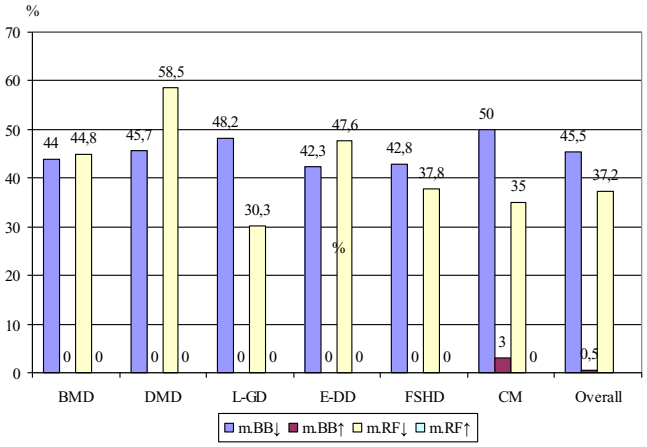

Fig. 2 – Abnormal mean MUAP duration in PMD and CM (% of muscles).
↓ – MUAP duration below the normal range.
↑ – MUAP duration above the normal range.

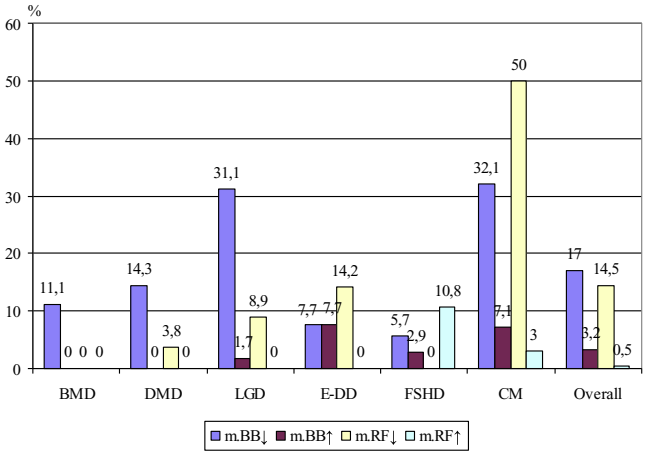

Fig. 3 – Abnormal mean MUAP amplitude in PMD and CM (% of muscles).
↓ – MUAP amplitude below the normal range.
↑ – MUAP amplitude above the normal range.

In the whole examined group, a reduced mean MUAP duration was recorded in 45.5% of BB and in 37.2% of RF muscles, most frequently in the DMD group (in 58.3% of BB muscles) (Fig. 2).

MUAPs with an increased mean duration and outliers with prolonged duration were observed in a few percent of all examined muscles.

A reduced mean MUAP amplitude was noted in 17% of BB and in 14.5% of RF muscles, most frequently in the CM group (in 50% of RF and in 32.1% of BB muscles, respectively) (Fig. 3). Outliers with a reduced amplitude were observed twice more frequently in BB comparing to RF muscles, most frequently in the DMD group (in 82.8% of BB and in 49.1% of RF muscles, respectively) (Fig. 4).

An increased mean MUAP amplitude was recorded in a few percent of all examined patients, and in no cases of DMD and

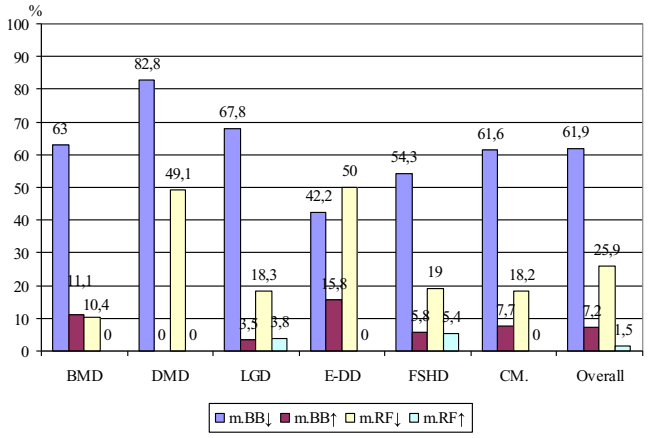

Fig. 4 – Outliers with amplitude out of the normal range in PMD and CM (% of muscles).
↓ – Amplitude below the normal range.
↑ – Amplitude above the normal range.

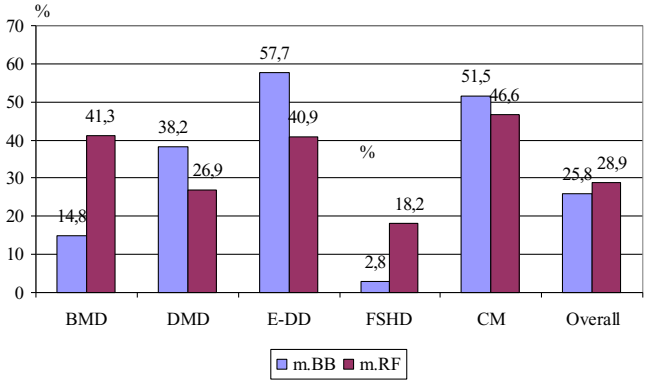

Fig. 5 – Polyphasicity in PMD and CM (% of muscles).

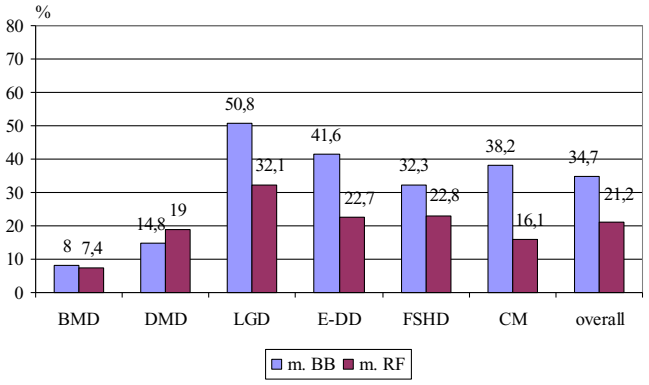

Fig. 6 – Pathological interference pattern during maximal muscle contraction in PMD and CM (% of muscles).

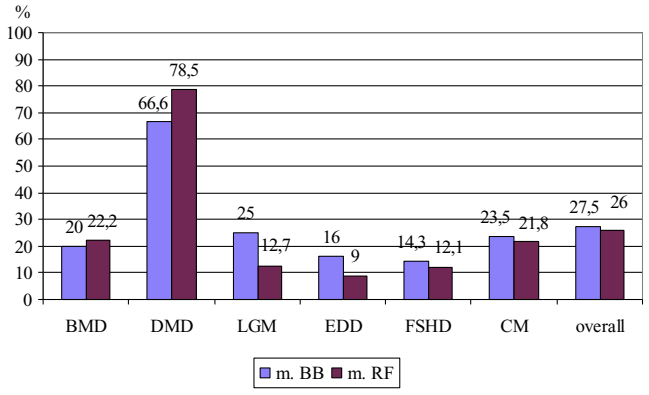

Fig. 7 – Amplitude of the interference pattern (range 0.1–0.5 mV) in PMD and CM (% of muscles).

BMD. Single potentials with an amplitude above the normal range were observed most frequently in E-DD and BMD patients (in 15.3% and 11.1% of BB muscles, respectively), and in no cases of DMD (Figs. 3 and 4).

In the whole examined group, an increased percentage of polyphasic potentials was recorded most frequently in E-DD patients (in 57.7% of BB muscles) (Fig. 5).

A pathological interference pattern during maximal muscle contraction was recorded in 34.7% of BB and 21.2% in RF muscles (Fig. 6).

A very low amplitude of the interference pattern (in the range of 0.1–0.5 mV) was observed most frequently in the DMD group (in 66.6% of BB and 78.5% of RF muscles, respectively) (Fig. 7).

In patients with FSHD, decreased mean MUAP duration, and SI were recorded more frequently in TA and DD muscles compared to BB and RF muscles (in 72.4% and 68.9% of TA muscles and in 55.8% and 50% of DD muscles, respectively). Mean values of MUAP parameters recorded in TA muscles differed significantly ($P < 0.05$) from the same parameters recorded in BB, DD and RF muscles.

Spontaneous activity was registered in a similar percentage of BB and RF muscles, most frequently in DMD and E-DD patients (in 34% of RF and 29.1% of BB muscles, respectively) (Fig. 8).

Logistic regression models (GLIMMIX procedure) showed that EMG results differed most between the DMD and E-DD groups.

The Fisher, Wilcoxon and Kruskal–Wallis tests showed a significantly higher frequency of decreased mean SI values and MUAP duration in DMD compared to BMD patients ($P < 0.0001$ and $P > 0.004$, respectively). A reduced mean

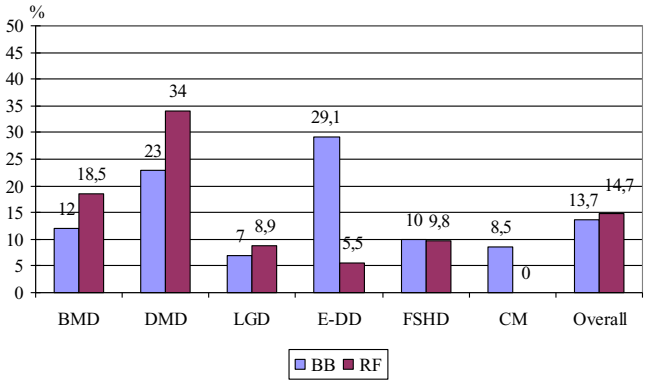

Fig. 8 – Acute denervation in PMD and CM (% of muscles).

amplitude and outliers with a reduced amplitude in BB and RF muscles were also observed more frequently in the DMD group than in the BMD group.

Comparison between the BMD and E-DD groups revealed a similar percentage (40%) of BB and RF muscles with a decreased mean MUAP duration, while outliers with a short duration in these two examined muscles were noted several times more frequently in the E-DD group compared to the BMD group (in 11.35% of BB muscles and 3.4% of RF muscles in BMD patients, and in 22.8% of BB muscles and 31.3% of RF muscles in E-DD patients, respectively). A reduced mean SI was observed more frequently in the E-DD group compared to the BMD group (88.9% and 55.1% of RF muscles, respectively). A reduced mean MUAP amplitude was observed in 10% of BB muscles in the BMD and E-DD groups, while an increased mean MUAP amplitude was observed in only 7.7% of BB muscles in the E-DD group.

A very low amplitude of maximal muscle effort (range 0.1–0.5 mV) was recorded significantly more frequently in the DMD group compared to the BMD group, and in the BMD group compared to the E-DD group (Fig. 7).

4. Discussion

Genetic tests are crucial for the diagnosis of congenital primary muscle diseases but EMG studies also remain very important. Features of a muscle potential such as its size and shape reflect the activity of the progression of muscle structure pathology [14,34,35].

Our EMG data obtained in PMD and CM generally fulfilled the criteria of a primary muscle lesion [15,17,20]. The most frequently changed EMG parameter was SI, estimating motor unit size, and a decreased mean SI value was recorded in more than 50% of BB and RF muscles. A reduced mean MUAP amplitude was observed in several percent of BB and RF muscles in the whole examined group, while ''outliers'' with an amplitude below the normal range were recorded in 61.9% of BB and 25.9% of RF muscles (in DMD in as many as 82% of BB muscles). In our opinion, these findings indicate a clear value of outliers, mainly in the first stage of the muscle disease when damage to the muscle structure is mild and limited.

Typical myopathic EMG recordings in PMD and CM were recorded more frequently in BB then in RF muscles. In the FSHD group, reduced mean MUAP duration, decreased SI, and the presence of a pathological interference pattern with a low amplitude were obtained most frequently in DD and TA muscles. These findings revealed that TA and DD muscles are more sensitive for muscle abnormalities, and thus they should be examined in all cases of suspected FSHD.

Decreased values of single potential parameters and a reduced amplitude of maximal effort were present more often in DMD compared to BMD, probably as a result of more acute and severe muscle structural damage, seen in muscle biopsy as a global reduction of muscle fiber number and diameter. In DMD, decreased membrane potential of persistent muscle fibers and a frequent absence of the initial and terminal phase of the potential cause shortening of MUAP duration and result in low values of MUAP amplitude.

A slow and mild course of BMD allows activation of muscle regeneration which is observed in EMG as the presence of single potentials with a high amplitude.

MUAPs with an increased mean amplitude and outliers with the amplitude above the normal range were recorded also in E-DD (nucleopathy). These high potentials, noted more frequently in E-DD than in BMD, are probably a result of the presence of multiple hypertrophic muscle fibers, their splitting, and in E-DD also due to a selective reduction in small-diameter type 1 muscle fibers. No typical features of neurogenic muscle lesion were observed in muscle biopsy performed in our patients with E-DD and BMD.

5. Conclusions

In summary, EMG recordings obtained in progressive muscular dystrophies and congenital myopathies revealed mostly typical myopathic changes, with the biceps brachii seemingly a more sensitive muscle for myopathic abnormalities. It was also confirmed that in FSHD, the obligatory muscles for EMG examinations are deltoid and tibial anterior muscles. Decreased values of MUAP parameters found more frequently in DMD compared to BMD confirmed a more active progression of the former.

Our analyses suggest that high amplitude MUAPs which are noted more frequently in E-DD and BMD could be a result of a chronic myopathic process with hypertrophy and splitting of muscle fibers. In addition, our study indicates a clear value of outliers, mainly in the first stage of muscle disease.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

[1] Bodensteiner J. Congenital myopathies. Muscle Nerve 1994;17:131–44.
[2] Bushby K. The limb-girdle muscular dystrophies. Diagnostic quidelines. Eur J Paediatr Neurol 1999;3:53–8.
[3] Dorobek M, Szmidt-Salkowska E. Dystrofia obreczowo-konczynowa i twarzowo-łopatkowo-ramieniowa. Polski Przegląd Neurol 2006;2(3):125–33.

[4] Dorobek M, Szmidt-Salkowska E. Nukleopatie emerynopatia, laminopatie Polski Przegląd. Neurologiczny 2006;2(3):134–7.
[5] Emery AEH. Emery–Dreifuss muscular dystrophy – a 40 year retrospective. Neuromuscul Disord 2000;10:228–32.
[6] Hausmanowa-Petrusewicz I, editor. Choroby nerwowo-mięśniowe. Lublin: Czelej; 2005.
[7] Drozdowski W, editor. Postępy w diagnostyce i leczeniu chorób mięśni. Kraków: Medycyna Praktyczna; 2004.
[8] Szmidt-Sałkowska E, Dorobek M. Nowe poglądy na patogenezę dystrofii mięśniowych postępujących. Polski Przegląd Neurol 2006;2(3):117–24.
[9] Tawil R, van der Maarel S. Facioscapulohumeral muscular dystrophy. Muscle Nerve 2006;34:1–14.
[10] Brown CA, Lanning RW, McKinney KQ, Salvino AR, Cherniske E, Crowe CA, et al. Novel and recurrent mutations in lamin A/C in patients with Emery–Dreifuss muscular dystrophy. Am J Med Genet 2001;102:359–67.
[11] Burgunder JM, Schols L, Baetsc J, Andersen P, Gasser T, Szolnoki Z, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. Eur J Neurol 2011;18:207–17.
[12] Fidziańska A, Toniolo D, Hausmanowa-Petrusewicz I. Ultrastructural abnormality of sarcolemmal nuclei in Emery–Dreifuss muscular dystrophy. J Neurol Sci 1998;159:88–93.
[13] Manilal S, Ngyyen TM, Sewry CA, Morris GE. Emery–Dreifuss muscular dystrophy protein emerin in a nuclear membrane protein. Hum Mol Genet 1996;5:801–8.
[14] Desmedt JE, editor. Progress in clinical neurophysiology. Basel: Karger; 1981.
[15] Fuglsang-Frederiksen A, Scheel U, Buchthal F. Diagnostic yield of the analysis of the pattern of electrical activity of muscle and of individual motor unit potentials in myopathy. J Neurol Neurosurg Psychiatry 1976;39: 742–50.
[16] Liguori R, Fuglsang-Frederiksen A, Nix W, Fawcett P, Andersen K. Electromyography in myopathy. Clin Neurophysiol 1997;27:200–3.
[17] Nandedkar S, Sanders D. Simulation of myopathic motor unit potentials. Muscle Nerve 1989;12(3):197–202.
[18] Podnar S, Zidar J. Sensitivity of motor unit potential analysis in facioscapulohumeral muscular dystrophy. Muscle Nerve 2006;34:451–6.
[19] Rowland L, DiMauro S, editors. Handbook of clinical neurology. Myopathies: Elsevier Science Publishers; 1992.
[20] Stubgen J. Limb girdle muscular dystrophy: a quantitative electromyographic study. Electromyogr Clin Neurophysiol 1995;35:351–7.
[21] Zalewska E, Rowińska-Marcińska K, Hausmanowa-Petrusewicz I. Shape irregularity of motor unit potentials in some neuromuscular disorders. Muscle Nerve 1998;21:1181–7.
[22] Nakashima K, Tabuchi Y, Takahashi K. The diagnositic significance of large action potentials in myopathy. J Neurol Sci 1983;61:161–70.
[23] Piotrkiewicz M, Hausmanowa-Petrusewicz I, Mierzejewska J. Are motoneurons involved in muscular dystrophy. Clin Neurophysiol 1999;110:1111–22.
[24] Rowinska-Marcińska K, Szmidt-Sałkowska E, Fidziańska A, Zalewska E, Dorobek M, Karwańska A, et al. Atypical motor unit potentials in Emery–Dreifuss muscular dystrophy (EDMD). Clin Neurophysiol 2005;116:2520–7.
[25] Uncini A, Lange D, Lovelace R, Solomon M, Hays A. Long-duration polyphasic motor unit potentials in myopathies: a quantitative study with pathological correlation. Muscle Nerve 1990;13:263–7.
[26] Dumitru D, King J, Nandedkar S. Motor unit action potentials recorded with concentric electrodes. Physiologic implications. Electroencephalogr Clin Neurophysiol 1997;105:333–9.
[27] Nandedkar S, Dumitru D, King J. Concentric needle electrode duration measurement and uptake area. Muscle Nerve 1997;20:1225–8.
[28] Sonoo M, Stålberg E. The ability of MUAP parameters to discriminate between normal and neurogenic MUPs in concentric EMG: analysis of the MUP thickness and the proposal of size index. Electroencephalogr Clin Neurophysiol 1993;89:291–303.
[29] Stalberg E, Bischoff C, Falck B. Outliers a way to detect abnormality in quantitative EMG. Muscle Nerve 1994;17:392–9.
[30] Bischoff C, Stålberg E, Falck B, Edebol K. Reference values of motor unit action potentials obtained with multi-MUAP analysis. Muscle Nerve 1994;17:842–51.
[31] Stalberg E, Nandedkar S, Sanders D, Falck B. Quantitative motor unit potential analysis. J Clin Neurophysiol 1996;13:401–22.
[32] Armitage P, Berry G, Matthews JNS. Statistical methods in medical research. 4th ed. Blackwell Science Ltd.; 2002.
[33] SAS Institute Inc.. 4th ed. SAS/STAT User's Guide Version 6, vol. 1,2, 4th ed. Cary, NC: SAS Institute Inc.; 1990.
[34] Emeryk-Szajewska B, Kopeć J. Electromyographic pattern in Duchenne and Becker muscular dystrophy. Part I: electromyographic pattern in subsequent stages of muscle lesion in Duchenne muscular dystrophy. Electromyogr Clin Neurophysiol 2008;48:265–77.
[35] Emeryk-Szajewska B, Kopeć J. Electromyographic pattern in Duchenne and Becker muscular dystrophy. Part II: electromyographic pattern in Becker muscular dystrophy in comparison with Duchenne muscular dystrophy. Electromyogr Clin Neurophysiol 2008;48:279–84.