Original research article

Peripheral nerve involvement in myotonic dystrophy type 2 – similar or different than in myotonic dystrophy type 1?

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ABSTRACT

Introduction: Multisystem manifestations of myotonic dystrophies type 1 (DM1) and 2 (DM2) are well known. Peripheral nerve involvement has been reported in DM1 but not in genetically confirmed DM2. The aim of our study was to assess peripheral nerve involvement in DM2 using nerve conduction studies and to compare these results with findings in DM1.

Methods: We prospectively studied patients with genetically confirmed DM2 (n = 30) and DM1 (n = 32). All patients underwent detailed neurological examination and nerve conduction studies.

Results: Abnormalities in electrophysiological studies were found in 26.67% of patients with DM2 and in 28.13% of patients with DM1 but the criteria of polyneuropathy were fulfilled in only 13.33% of patients with DM2 and 12.5% of patients with DM1. The polyneuropathy was subclinical, and no correlation was found between its presence and patient age or disease duration.

Conclusions: Peripheral nerves are quite frequently involved in DM2, but abnormalities meeting the criteria of polyneuropathy are rarely found. The incidence of peripheral nerve involvement is similar in both types of myotonic dystrophy.

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1. Introduction

Muscular dystrophies are inherited, progressive, degenerative disorders of skeletal muscles. Myotonic dystrophies (DM) are characterized by two important additional features: myotonia (the phenomenon which can be seen clinically and electrophysiologically) and extramuscular multisystem involvement. Both these features can lead to large variability of the clinical presentation. Two different types of myotonic dystrophies,
type 1 (DM1, first described by Steinert) and type 2 (DM2, previously termed proximal myotonic myopathy, PROMM), are currently distinguished. Although DM1 and DM2 are similar in terms of extramuscular system involvement, there are also some clinical differences which help to distinguish them from each other, most importantly age at the onset of the disease, the pattern of muscle weakness, absence of congenital and childhood-onset forms of DM2, and limited evidence of central nervous system (CNS) involvement in DM 2 [1,2].

Myotonic dystrophy type 2 (DM2) is an autosomal dominant disorder caused by an expansion of the CCTG repeat in the first intron in the ZNF 9 gene encoding zinc finger protein 9 [3]. DM2 is a multisystem disorder characterized by myotonia and muscle weakness. The weakness typically affects proximal muscles, in contrast to DM1 which initially affects distal upper limb muscles. The onset of weakness is relatively late, most often in the fourth or fifth decade of life [4]. DM2 is also a clinically milder disease that DM1, with fewer patients requiring assistive devices [5], no cases of respiratory failure reported to date [1] and almost normal life expectancy [4]. Most patients complain of muscle pain which seems to be independent of the severity of myotonia and exercise intensity, and may be the most disabling symptom [6]. Other characteristic signs and symptoms of DM2 are general fatigue and calf hypertrophy [2,5]. Extramuscular clinical features include cardiac conduction defects, cataract, endocrine changes including testicular failure and diabetes mellitus [4–6], and cognitive symptoms such as problems with organization, concentration and word finding which are considerably milder then in DM1 [5–7]. DM2 patients are also generally spared from complications of general anesthesia [2,4]. To the best of our knowledge, the peripheral nervous system involvement has not been reported until now in genetically confirmed DM2.

Myotonic dystrophy type 1 (DM1) is also an autosomal dominant disease caused by an unstable CTG repeat expansion in the 3′ untranslated region of the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19q13.3 [8]. It is the most common muscular dystrophy in adult life, presenting with a wide spectrum of extramuscular symptoms, e.g. cataract, frontal balding, cardiac conduction abnormalities, testicular atrophy with associated reduced fertility, diabetes mellitus, and irritable bowel-like symptoms [1,2,5,6,9–11]. There is also evidence for CNS involvement with cognitive impairment/mental retardation, psychological dysfunction or excessive daytime sleepiness [1,2,5,12]. The issue of peripheral nerve involvement in DM1 is still a matter of debate. Although patients seldom complain of sensory symptoms, some authors described peripheral neuropathy [13–18] or abnormal results of peripheral nerve conduction studies [19–22] in patients with DM1. Other reports, however, indicate no primary peripheral nervous system involvement in DM1 [23–26]. Some experimental studies in animal models of DM1 suggested that peripheral motor neuropathy can be linked to a large CTG expansion and a more severe form of DM1 [27]. This is consistent with previous reports showing an increasing severity of neuromuscular involvement in the affected members of consecutive generations, which can be explained by anticipation [28]. However, the majority of these studies are of limited value due to small sample size, lack of genetic confirmation or no definitions of peripheral neuropathy. A larger study by Hermans et al. [29] showed electrophysiological abnormalities meeting criteria of peripheral neuropathy in 16/93 patients (17%) with genetically confirmed DM1 but the course of neuropathy in these patients was subclinical.

2. Methods

We prospectively studied patients with genetically confirmed DM2 (n = 30) and DM1 (n = 32). Molecular evaluation for DM1 and DM2 included two-step analysis with standard polymerase chain reaction (PCR) and repeat primed PCR (RP-PCR) method applied for detection of long expansions, originally developed as triplet primed PCR (TP-PCR) for the molecular analysis of DM1 [30]. This diagnostic approach has been recommended by the European Molecular Quality Network (EMQN Best Practice Guidelines and Recommendations on Myotonic Dystrophy type 1 and 2). All but one DM1 patients carried expansions above 100 CTG repeats (detected by RP-PCR) and a single case harbored 75 CTG within the range amplifiable by standard PCR. In normal DM2 alleles, the complex size ranges from 104 to 176 bp which is usually reported in base pairs length due to highly polymorphic TG and TCTG repeat tracts. In all 30 DM2 patients, the presence of expansions was confirmed by RP-PCR.

Patients were evaluated at the Department of Neurology, Medical University of Warsaw. The DM2 group included 16 women (53.33%) and 14 men (46.67%) with the mean age of 47.65 ± 11.92 years (range 25–63), and the DM1 group included 10 women (31.25%) and 22 men (68.75%) with the mean age of 36.9 ± 12.35 years (range 10–64). The mean estimated disease duration was 11.92 ± 8.83 years (range 2–31) in the DM2 group and 9.42 ± 7.68 years (range 1–49) in the DM1 group. The mean age at the time of overt clinical manifestation was 36.27 ± 13.54 years (range 12–60) and 27.52 ± 14.09 years (range 1–50), respectively. In the DM2 group, the most common symptoms were muscle weakness (40%), muscle stiffness (32.5%) and muscle pain (26.67%), while muscle weakness (62.5%) and muscle stiffness (31.25%) were the most common symptoms in the DM1 group. Two patients in the DM2 group and 4 patients in the DM1 group had diabetes mellitus (type 2 in five of these patients). Moreover, a history of hypothyroidism was noted in four patients with DM2 and one patient with DM1. Both concomitant diseases were well controlled (with normal results of laboratory tests), patients did not complain of symptoms characteristic for polynuropathy (PNP), and there were no signs of polynuropathy on neurological assessment. Other known causes of PNP (e.g. renal insufficiency or vitamin B12, B6 and B1 deficiency as well as a history of alcohol abuse or chemotheraphy) were excluded.

All patients underwent detailed neurological examination performed by an experienced neurologist from the Neuromuscular Unit of our Department. Muscle strength was assessed using the Medical Research Council (MRC) scale. The following muscles were tested: neck flexors and extensors (sternocleidomastoideus, trapezius) and 14 bilateral muscles (deltoides, biceps and triceps brachii, extensor carpi radialis, flexors digitorum, ilipsoas, quadriceps, rectus and biceps femoris, semitendinosus, tibialis anterior, extensor digitorum
longus, gastrocnemius, soleus). The MRC compound score was calculated by adding results for the tested muscles (from proximal and distal muscles, lower and upper extremities separately) and dividing by the sum of the number of muscles tested. Upper extremities proximal MRC compound score was calculated by adding the MRC scores of bilateral shoulder abductors, elbow flexors and elbow extensors divided by the number of muscles tested (n = 6) whereas upper extremities distal MRC compound score was calculated by adding the MRC scores of bilateral wrist extensors and digit flexors divided by the number of muscles tested (n = 4). Similarly in lower limbs: lower extremities proximal MRC compound score was calculated by adding the MRC scores of bilateral hip flexors, knee flexors and knee extensors divided by the number of muscles tested (n = 10) and lower extremities distal MRC compound score – by adding the MRC scores of bilateral ankle dorsiflexors and ankle plantar flexors divided by the number of muscles tested (n = 8).

Deep tendon reflexes were scored as exaggerated (3), normal (2), diminished (1) or absent (0). Pinprick, touch, vibration as well as joint position sense were evaluated. The clinical investigation also included a number of questions referring to the most common symptoms of PNP. The study protocol was approved by the Ethics Committee at the Medical University of Warsaw (No. KB 180/2008). A written informed consent was obtained from all patients before ENG examination.

2.1. Nerve conduction studies

Electrophysiological studies were performed using the Keypoint EMG system (Medtronic Functional Diagnostics). Motor nerve conduction studies (MNCS) were performed unilaterally with supramaximal surface stimulation on the median, ulnar, and peroneal nerves and recording from the abductor pollicis brevis, abductor digiti minimi and extensor digitorum brevis, respectively. The F wave, an index of stimulus conduction in the proximal part of lower motor neuron (spinal roots and the proximal region of the peripheral nerves), was measured from the median, ulnar and peroneal nerves. Sensory nerve conduction studies (SNCS) were also performed unilaterally with surface orthodromic stimulation on the median, ulnar and sural nerves. Skin temperature was measured and maintained above 32 °C. All amplitude values were measured as negative peak. The results were obtained by a neurologist experienced in EMG who was blinded for other patient data. All nerve conduction parameters were compared to the normal values adopted in our EMG laboratory (matched for age, gender and height) and considered abnormal if differed from the mean values by more than two standard deviations (SD).

An electrophysiological diagnosis of PNP (modified from Oh [31]) was established when:

1. conduction velocity and/or prolonged distal latency were abnormal in at least two separate motor nerves and/or
2. amplitude of the sensory nerve action potential (SNAP) and/or conduction velocity were abnormal in at least two separate sensory nerves.

For the diagnosis of PNP, the amplitude of the compound muscle action potential (CMAP) was not taken into account because it can be independently affected by the myogenic process.

Moreover, we excluded from the study the patients with entrapment neuropathies, especially carpal tunnel syndrome, confirmed according to the American Association of Electrodagnostic Medicine (AAEM, 2002) (comparison of sensory latency of median nerve across the wrist with ulnar sensory conduction across the wrist in the same limb or definite conduction block under carpal tunnel; if necessary comparison of the median nerve distal latency – second lumbrical to the ulnar motor nerve distal latency – second interossei).

2.2. Statistical analysis

Statistical analysis included descriptive statistics (mean values and SD or median values and ranges) and the Wilcoxon test or the Fisher’s exact test for comparisons of variables between groups. A generalized linear model (GLM) taking into account gender and age was used for comparisons between the DM1 and DM2 groups. All analyses were performed using the SAS software, version 9.3. P < 0.05 was considered statistically significant.

3. Results

The demographic profile of the two studied groups differed significantly: patients in the DM2 group were about a decade older than patients in the DM1 group (p < 0.001) and the majority of them were female (53.33% in the DM2 group vs 31.25% in the DM1 group; p < 0.05).

Patients in the DM2 group had predominant proximal limb weakness, while all DM1 patients had predominant distal limb weakness. The demographic and clinical characteristics of the two groups are shown in Table 1.

Based on responses to questions referring to the most common symptoms of PNP, no patient from either study group reported positive or negative sensory symptoms characteristic for the diagnosis of PNP. Pinprick, touch, vibration as well as joint position sense were normal in all patients. Tendon reflexes were exaggerated in five patients, diminished in three patients, and absent in two patients in the DM2 group. In the DM1 group, they were diminished in 16 patients and absent in 6 patients.

Results of the electrophysiological studies (MNCS and SNCS) are presented in Table S1 (see supplementary materials).

When results obtained in DM2 and DM1 patients were compared to the normal values adopted in our EMG laboratory (matched for age, gender and height), nonsignificant trends were noted for reduced amplitude, increased latency and decreased CV in SNCS in the median nerve among patients with DM2 (23.08% vs. 6.06%, 23.08% vs. 12.12%, and 11.54% vs. 0%, respectively, in DM2 compared to DM1). A decrease in CMAP amplitude in the median nerve was significantly more often seen in patients with DM1 (p < 0.05, Fisher’s exact test). Taking into account more distal distribution of symptoms in DM1, we cannot exclude that this parameter may be independently affected by the myopathic process. A surprising finding was decreased CV across the elbow in the ulnar nerve.
Table 1 - Demographic and clinical characteristics of the DM1 (n = 32) and DM2 (n = 30) groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DM1 (n = 32)</th>
<th>DM2 (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>22/10</td>
<td>14/16</td>
</tr>
<tr>
<td>Age, years (mean ± SD; range)</td>
<td>36.9 ± 12.35 (10-64)</td>
<td>47.65 ± 11.92 (25-63)</td>
</tr>
<tr>
<td>Age at disease onset, years</td>
<td>27.52 ± 14.09 (1-50)</td>
<td>36.27 ± 13.54 (12-60)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>9.42 ± 7.68 (1-40)</td>
<td>11.92 ± 8.83 (2-31)</td>
</tr>
<tr>
<td>UE proximal MRC compound score</td>
<td>4.52 ± 0.68 (3-5)</td>
<td>4.57 ± 0.50 (3-5)</td>
</tr>
<tr>
<td>LE proximal MRC compound score</td>
<td>4.02 ± 0.76 (2-5)</td>
<td>4.84 ± 0.36 (4-5)</td>
</tr>
<tr>
<td>UE distal MRC compound score</td>
<td>4.63 ± 0.61 (3-5)</td>
<td>4.27 ± 0.63 (2-5)</td>
</tr>
<tr>
<td>LE distal MRC compound score</td>
<td>3.75 ± 1.09 (1-5)</td>
<td>4.60 ± 0.53 (3-5)</td>
</tr>
</tbody>
</table>

Abbreviations: DM1, myotonic dystrophy type 1; DM2, myotonic dystrophy type 2; SD, standard deviation; MRC, Medical Research Council; UE, upper extremities; LE, lower extremities.

Table 2 - Demographic and clinical characteristics of the DM1 and DM2 patients with or without electrophysiologically confirmed PNP.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PNP present (n = 4)</th>
<th>PNP absent (n = 28)</th>
<th>PNP present (n = 4)</th>
<th>PNP absent (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td></td>
<td></td>
<td>3/1</td>
<td>12/15</td>
</tr>
<tr>
<td>Age, yrs (mean ± SD; range)</td>
<td>40.0 ± 12.27(29-50)</td>
<td>36.89 ± 12.65(10-64)</td>
<td>50.25 ± 13.15(37-63)</td>
<td>47.18 ± 11.95(25-63)</td>
</tr>
<tr>
<td>Age at disease onset, yrs</td>
<td>23.67 ± 14.15(15-40)</td>
<td>27.93 ± 14.28(1-5)</td>
<td>39.75 ± 20.98(15-60)</td>
<td>35.64 ± 12.35(12-60)</td>
</tr>
<tr>
<td>Disease duration, yrs</td>
<td>13.33 ± 3.51(10-17)</td>
<td>9.01 ± 7.93(1-40)</td>
<td>11.75 ± 7.85(3-22)</td>
<td>11.95 ± 9.17(2-31)</td>
</tr>
<tr>
<td>UE proximal MRC compound score</td>
<td>4.58 ± 0.46(4-5)</td>
<td>4.51 ± 0.71(3-5)</td>
<td>4.51 ± 0.50(4-5)</td>
<td>4.58 ± 0.49(4-5)</td>
</tr>
<tr>
<td>UE distal MRC compound score</td>
<td>3.80 ± 0.42(3-5)</td>
<td>4.04 ± 0.79(3-5)</td>
<td>4.71 ± 0.47(4-5)</td>
<td>4.86 ± 0.34(4-5)</td>
</tr>
<tr>
<td>LE proximal MRC compound score</td>
<td>4.78 ± 0.36(4-5)</td>
<td>4.62 ± 0.63(3-5)</td>
<td>4.37 ± 0.61(3-5)</td>
<td>4.25 ± 0.64(2-5)</td>
</tr>
<tr>
<td>LE distal MRC compound score</td>
<td>3.83 ± 1.12(2-5)</td>
<td>3.74 ± 1.09(1-5)</td>
<td>4.55 ± 0.53(3-5)</td>
<td>4.61 ± 0.54(3-5)</td>
</tr>
</tbody>
</table>

Abbreviations: DM1, myotonic dystrophy type 1; DM2, myotonic dystrophy type 2; PNP, polyneuropathy; yrs, years; SD, standard deviation; MRC, Medical Research Council; UE, upper extremities; LE, lower extremities.

In 11/32 (34.38%) patients with DM1 compared to no case among DM2 patients (p < 0.05, Fisher’s exact test). A trend for decreased CMAP amplitude in the peroneal nerve as well as reduced CV in SNCS in the ulnar nerve was also observed in the DM1 group (21.43% vs. 9.68% and 12.5% vs. 4.35%, respectively, in DM1 compared to DM2).

Abnormal results of the electrophysiological studies were found in 8/30 (26.67%) patients in the DM2 group. The most frequent findings included decreased SNAP amplitude in the median nerve (6/8 patients, 75.0%) and in the ulnar nerve (4/8 patients, 50.0%). Decreased sensory CV in the median nerve and increased F-wave latency in the peroneal nerve (both in 2/8 patients; 25.0%) were also found. In 4/8 patients, we observed only one abnormality in nerve conduction studies, most commonly reduced SNAP amplitude in the ulnar or median nerve. In the remaining 4 patients, PNP was diagnosed according to the above mentioned electrophysiological criteria. Thus, the estimated incidence of PNP (with subclinical changes only) in our DM2 group was 13.33%. Only in one of these patients with PNP, an abnormality of the thyroid gland had been diagnosed in the past, but normal thyroid function was ascertained at the time of EMG examination. The demographic and clinical characteristics of the DM2 patients with or without confirmed PNP are shown in Table 2.

Abnormal results of nerve conduction studies were obtained in 9/32 (28.13%) patients in the DM1 group. The most frequent findings included decreased SNAP amplitude (5/9 patients, 55.56%) and decreased sensory CV (4/9 patients, 44.44%) in the ulnar nerve as well as increased F-wave latency and decreased motor CV in the median nerve (both in 2/9 patients; 9.88%). We did not find decreased motor CV across the elbow in the ulnar nerve in any of the patients with abnormal parameters of SNCS in this nerve. In 5/9 patients, we observed only one abnormality in nerve conduction studies (most often decreased CV in the ulnar or median nerve or increased latency of the F-wave in the peroneal nerve). In the other four patients, PNP was diagnosed according to the above mentioned criteria, and thus the incidence of PNP in DM1 (with subclinical changes only) can be estimated at 12.5%. Only one of these patients with PNP had a prior history...
of well-controlled diabetes mellitus. The demographic and clinical characteristics of the DM1 patients with or without confirmed PNP are shown in Table 2.

When results obtained in both groups were compared using statistical generalized linear models that included age and gender as confounding factors, a few significant differences were found: distal latency and F-wave latency in the median nerve were longer in the DM2 group ($p < 0.05$ for both), and distal latency in the peroneal nerve was in longer in the DM1 group ($p < 0.05$) but all mean values in both groups were within normal limits. In addition, we found lower values of SNAP amplitude in the median nerve in DM2 patients ($p < 0.001$) and longer latency of SNAP in the sural nerve in DM1 patients ($p < 0.05$), again with all mean values in both groups within normal limits. We also noted a nonsignificant trend for longer F-wave latency (but still within normal limits) in the peroneal nerve in the DM2 group compared to the DM1 group.

### 4. Discussion

Our DM2 patients were significantly older than patients in the DM1 group. Similar age differences, albeit statistically nonsignificant, was reported by Logigian et al. [32]. This age difference is sufficiently explained by a more severe disease course of DM1 which makes patients seek help earlier and thus the diagnosis is made at a younger age.

Normal results of nerve conduction studies in DM2 patients have been usually reported in the literature [1,2,5,6]. In our group, however, we found some abnormal results of electrophysiological studies in nearly 27% of patients with DM2. The most frequent findings included decreased SNAP amplitude in the median and ulnar nerve. The electrodagnostic criteria for entrapment neuropathies of the upper limb were not fulfilled. On the other hand, we could diagnose PNP according to the above mentioned electrophysiological criteria in only 4 patients (13.33%) [31]. PNP was mostly of sensory and axonal character and the changes were subclinical in the majority of patients. Two patients in the DM2 group had diabetes mellitus (type 1 in one of them) and a history of hypothyroidism was noted in four patients but among the four patients with PNP, abnormal thyroid function had been diagnosed in the past only in one patient, and a euthyroid state was ascertained at the time of the study. This suggests that peripheral nerve dysfunction in our DM2 patients was independent of other metabolic factors and is most likely primary. Moreover, in another 4 patients we observed only one abnormality in nerve conduction studies, which was not sufficient to diagnose PNP. The most common abnormalities were reduced SNAP amplitudes in the ulnar and median nerve. The authors have not encountered any description of peripheral nerve involvement in genetically confirmed DM2 in the literature. In most recently published reviews [2,6], normal nerve conduction study results are considered a feature of DM2. In a study by Dabby et al. [33], neuropathy was found in 2 of 10 patients with genetically confirmed DM2, but the criteria for the diagnosis of PNP were not listed and the patient sample was very small.

Some electrophysiological studies of DM1 suggest that the incidence of PNP ranges from 18% [17] to 45% [14], and on average is 20–30% [13,15,16]. In a recent study of 93 patients with DM1, Hermans et al. [29] found evidence of PNP in 17% of patients using clearly defined electrophysiological criteria. The presence of PNP in DM1 was also confirmed by pathological studies showing involvement of sensory fibers [25,34–36]. In our study, we were able to diagnose PNP based on the electrophysiological criteria mentioned in the Methods section [31] in only 12.5% patients with DM1. Some other reports, however, indicated no PNP in DM1 by showing normal or near normal results of conduction studies [23–25]. These conflicting results could be attributed to varying patient populations (number of investigated patients, lack of genetic confirmation), different electrophysiological methods or specific protocols used (e.g., type of electrodes or needles, number of limbs or nerves tested, motor/sensory nerves only). In a histological study on transgenic DM300 mice, no evidence of nerve fiber involvement was found [26]. Some authors indicated that conflicting results could result from different lengths of CTG repeats in DM 1 patients. This notion may be supported by studies performed in transgenic DMSXL mice carrying a larger CTG expansion and expressing more severe DM1 phenotype than DM300 mice, with definite histologic and electrophysiological features of peripheral neuropathy [27].

Polyneuropathy in DM1 is described in most cases as an axonal sensory or sensorimotor neuropathy characterized by decreased CV and/or reduced SNAP amplitudes [13–17, 20–22,29]. In our study, the most common abnormal electrophysiological findings in patients with DM1 included decreased SNAP amplitude and decreased CV in the ulnar nerve as well as increased F-wave latency and decreased CV in the median nerve which allowed us to categorize the PNP in DM1 as a mostly sensory axonal neuropathy, similarly to the DM2 group.

In most cases reported in the literature, PNP was revealed by the electrophysiological examination, without patient complain or marked symptoms in neurological examination, suggesting its mild or even subclinical nature. Also in our study, none of the patients with PNP complained of sensory symptoms and neurological examination of sensation was normal in all patients. Thus, PNP in these patients may be considered subclinical, which is consistent with recently published reports [18,29].

The presence of PNP did not correlate with patient age or disease duration in any of the studied groups. Our findings are consistent with some previously published reports [13,15,20,29], although such an association was found in other studies [14,18,21]. According to Logullo et al. [14] a more severe clinical picture of DM1 was significantly associated with the presence of PNP but the degree of nerve conduction abnormalities did not correlate with the severity of myopathy and clinical impairment, thus suggesting independent muscle and nerve involvement. The observation that PNP tends to progress irrespective of the clinical severity of myopathy was also confirmed by other authors [15,18,20]. More recently, however, Hermans et al. [29] found a correlation between peripheral nervous system involvement, decreased muscle strength, and absence of Achilles tendon reflexes.

Another unsettled issue regarding peripheral nervous system involvement in DM1 is its primary or secondary nature. Some authors supported the notion of primary peripheral nerve
dysfunction in DM1 which is unrelated to glucose intolerance or other metabolic factors [14,16,17,20,29,37]. Studies performed in transgenic mice (DMSXL) also demonstrated the presence of motor neuropathy. This neuropathy seemed to be independent of abnormalities of the thyroid gland or the pancreas because neuropathy did not develop in transgenic DM300 mice used to generate DMSXL mice [26,27].

In our study, four patients in the DM1 group had diabetes mellitus type 2 and a history of hypothyroidism was noted in one patient, but diabetes was identified in only one of 4 patients with polyneuropathy and the condition was well controlled. This observation may support the notion of primary peripheral nerve dysfunction in DM1.

In five of nine DM1 patients with abnormal results of nerve conduction studies, only one abnormality was observed which was not enough to establish the diagnosis of PNP. The most common abnormal findings were decreased CV along the whole ulnar and median nerve (not only within entrapment sites) as well as increased latency of the F-wave in the peroneal nerve. Similar results were reported in a study by Bae et al. [17] in which 8 of 18 patients had abnormal nerve conduction study findings (most common were abnormal peroneal motor nerve conduction and the H-reflex) but a sensorimotor axonal polyneuropathy was diagnosed only in one patient. Bae et al. [17] suggested that some minimal abnormalities found in conduction studies (which did not allow the diagnosis of PNP) could also be explained by technical factors (e.g., muscle wasting) or concomitant conditions such as lumbosacral polyradiculopathy.

The aim of our study was also to compare the nerve conduction study results in DM1 and DM2 and a number of significant differences was found between these two groups. Distal latency and F-wave latency in the median nerve were longer in the DM2 group, while longer distal latency in the peroneal nerve was seen in the DM1 group. In addition, SNCS also revealed lower values of SNAP amplitude in the median nerve in DM2 patients and longer latency of SNAP in the sural nerve in DM1 patients. Of note, however, all mean values in both studied groups were within normal limits. We also noted a nonsignificant trend for longer F-wave latency (but not within normal limits) in the peroneal nerve in the DM2 group compared to the DM1 group.

We identified only one report in the literature that compared DM1 and DM2 from the neurophysiological point of view [32]. The aim of that study was to evaluate the severity, type and distribution of myotonic discharges in both types of myotonic dystrophy and the authors did not report nerve conduction study results. Our results indicate that abnormalities in nerve conduction studies in both types of myotonic dystrophy occur at a similar rate (25–30%). Thus, examination of the peripheral nerves seems not to be very useful when differentiating between DM1 and DM2.

In our study, we quite frequently encountered electrophysiological evidence of some kind of peripheral nerve involvement in both types of myotonic dystrophy. However, we were able to diagnose PNP based on NCS in only 13.3% of patients with DM2 and in 12.5% of patients with DM1. It is of interest that none of our patients with PNP complained of sensory symptoms and neurological examination of sensation was normal in all patients. Thus, PNP in both types of myotonic dystrophy may be considered subclinical and categorized as sensory axonal based on nerve conduction study results. We also believe that the peripheral nervous system involvement is unrelated to other metabolic or endocrine diseases such as diabetes mellitus or hypothyroidism. This may support the notion of primary peripheral nerve dysfunction in DM2 and DM1.

In conclusion, this is the first study to prove the presence of peripheral nerve involvement in genetically confirmed DM2, although its degree may be minor, like in DM1. Peripheral nerves are quite frequently involved in both types of myotonic dystrophy (with a similar incidence of about 25–30%) but abnormalities fulfilling the electrophysiological criteria of PNP are rarely found (in about 13% of cases). As PNP in DM2 and DM1 may be expected to be subclinical, other causes of peripheral nerve involvement should be considered when symptoms of a marked sensory or sensorimotor PNP are found in the neurological or electrophysiological examination.

Conflict of interest

None declared.

Acknowledgement and financial support

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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; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pjnsa.2015.04.008.

References


