The Character and Frequency of Muscular Pain in Myotonic Dystrophy and Their Relationship to Myotonia

Olesja Parmová1,3*, Stanislav Voháňka1,3 and Jana Strenková2

1Department of Neurology, University Hospital and Masaryk University, Czech Republic
2Institute of Biostatistics and Analyses, Masaryk University, Czech Republic
3Central European Institute of Technology, CEITEC MU, Masaryk University, Czech Republic

*Corresponding author: Olesja Parmová, Department of Neurology, University Hospital, Jihlavská 20, 625 00 Brno, Czech Republic, Fax: 532 232 249; E-mail olesja.parmova@fnbrno.cz

Abstract

Background: Myotonic dystrophy is the most common form of muscular dystrophy in adults. Pain is reported in various hereditary muscular diseases at a frequency of 64%–83%.

Methods: A group of 70 patients with myotonic dystrophy (21 persons with type 1 and 49 with type 2) was investigated by means of questionnaires structured around the subject of pain.

Results: The frequency of long-term muscle pain was 57% in patients suffering from myotonic dystrophy type 1 and 55% among those with type 2. Presence of pain at examination was reported by 52% of patients with myotonic dystrophy type 1 and 59% of patients with type 2. The pain intensity appeared almost identical in the two groups. In terms of pain descriptors, a significant difference was found only in the “gnawing” pain category. The pain reported most often fell into the “aching” and “tiring/exhausting” descriptors.

Conclusions: We found no significant differences in the frequency, quality and severity of pain between the different types of the disease.

Keywords

Myotonic dystrophy, Myotonia, Muscular pain, Frequency, Quality of life

Introduction

Myotonic Dystrophy (DM) is the most common form of muscular dystrophy in adults. It is a multisystem disease characterized by slowly progressive weakness of the skeletal muscles, myotonia, and the further involvement of a number of organ systems. The disease has an autosomal dominant pattern of inheritance and it is divided into two genetically distinct forms: type 1 (DM1) and type 2 (DM2). In both forms, molecular genetic analysis indicates distinct microsatellite expansions that occur in the non-coding regions of certain genes, specifically expanded and unstable trinucleotide (CTG) repeat, localized to the 3’ untranslated region of the dystrophy myotonia-protein kinase (DMPK) gene on chromosome 19q13.3 (DM1) and expanded and unstable tetranucleotide (CCTG) repeat in nuclear acid binding protein (CNBP) gene on chromosome 3q21.3 (DM2, previously known as the zinc finger 9 (ZNF9) gene [1-3]. In both cases, the gene including the abnormal repeat expansion is transcribed into RNA but not translated into protein. The mutant RNA accumulates in the nucleus and disturbs the function of RNA-binding proteins, and this disrupts the function of many different genes, including those coding for the muscle-specific chloride channel ClC-1, giving rise to the multiple symptoms typical of the DM [4].

The disorder manifests as progressive muscle weakness, together with myotonia (delayed relaxation of skeletal muscles) that typically subsides after repetitive movements (warm-up phenomenon) and is usually exacerbated by cold [5] and further by multi-organ involvement (cardiac arrhythmia, cardiomyopathy, subcapsular cataract, respiratory insufficienty, digestive disorders, diabetes mellitus, testicular atrophy, and more).

The incidence of the disease (DM1) is estimated at 1 in 8,000 (12.5 per 100,000) births, although worldwide estimates of prevalence vary widely between different geographical and background-specific populations, between 0.5 and 18.1 per 100,000 [6-8]. A high prevalence of DM2 mutations has been reported in the population of Finland: 54.6 per 100,000 inhabitants. The authors of this study suggest that DM2 patients are under-diagnosed, with the fact that symptoms frequently occur in the elderly population making a particular contribution [6]. In most of the population, type 1 DM appears to be more common than type 2. However, certain recent studies suggest that type 2 may be as common as type 1, and perhaps even more frequent [6,9].

Pain is common among patients with slowly progressive neuromuscular disorders. Its incidence has varied in the literature recording this process. Pain is reported in the various hereditary muscular disorders at an incidence of 64% - 83% [10-16]. Many similarities in the nature and severity of such pain exist, but important differences have also been identified among the diagnostic groups of neuromuscular diseases [14]. Pain is often a symptom for patients with myotonic dystrophy; it may fluctuate over time and can be influenced by exercise, palpation, and temperature [17-19]. Patients
complain of various types of pain, myalgia and cramps, most often located in the thighs, back and proximal upper limbs [9,19]. Pain is also an important indicator of the onset of DM2 [20].

The purposes of this study are to determine the frequency of muscle pain among patients with myotonic dystrophy and to compare the character of such pain in type 1 and type 2 DM. Further, the study seeks to determine whether the pain is related to myotonia and to evaluate any differences in the frequency of muscle pain among patients with and without myotonia. This is the first extensive study to make a comparison of the frequency of pain between the two types of myotonic dystrophy.

Patients and Methods

Patients

Seventy consecutive patients entered into the Czech national registry of muscular dystrophy (ReaDy) were investigated in the course of routine annual examinations by means of questionnaires based on pain and quality of life, in addition to motor function assessment on the Medical Research Council (MRC) scale [21,22], a 6-minute walk test (6mWT) [23], spirometry, and cardiological and ophthalmological examination. The Czech ReaDy register was established in 2011, its structure based on that of existing international counterparts, and includes four muscle diseases (Duchenne/Becker muscular dystrophy, myotonic dystrophy, spinal muscular atrophy and facioscapulohumeral muscular dystrophy). Genetically confirmed patients have been recruited into the registry at nine neuromuscular centers since June 2011. Genetic test result that confirmed mutation on the affected gene is exclusive criterion for inclusion patients to the registry and to the study. Patients are examined around once a year. All patients signed informed consent to participate in the study. This study included all patients regardless of degree of disability, from the mildly symptomatic to the severely weak.

Measurements

Muscle pain was investigated by means of a short form of the McGill pain questionnaire (SF-MPQ) [24,25] and the short form of brief pain inventory questionnaire (BPI) [26-28]. SF-MPQ is designed to investigate the pain experience in qualitative terms. The test includes 15 descriptors of pain (11 sensory, 4 affective), rated on an intensity scale of 0–none, 1=mild, 2=moderate and 3=severe. SF-MPQ also includes current pain intensity (at examination) and a visual analogue scale of pain in the previous week. BPI allows patients to rate the severity of their pain and the degree to which that pain interferes with common aspects of feeling and function. BPI uses 100mm horizontal line with word descriptors at each end (“no pain” and “the worst possible pain”). Patients were asked to rate pain intensity by placing a mark on this scale.

In this study the assessment of long-term pain was evaluated as pain that had been present for longer than a year.

The quality of life questionnaire (SF-36) [29,30] was also used in this study to detect the influence of pain. SF-36 is a multi-purpose test, a short-form health survey with only 36 questions.

Myotonia is defined as delayed relaxation of skeletal muscle after voluntary contraction or percussion. In the course of examination, the testing of myotonia was performed by one of the authors (OP) and myotonia was identified by asking patients to repeatedly grip and release the examiner’s fingers, or was provoked by percussion of muscle, mostly at the thenar eminence, and/or myotonia was identified through patient’s descriptions of muscle stiffness. The degree of myotonia was divided into “mild” and “severe”. “Severe” myotonia was identified as the inability to release the examiner’s fingers immediately after the strong grip. The other less strong degrees of stiffness or delayed relaxation were assigned as “mild” myotonia.

Statistical approaches

Standard descriptive statistics were applied in the analysis of results: mean standard deviation and median supplemented by 5th–95th percentile range for continuous variables and absolute and relative frequencies for categorical variables. The statistical significance of differences among groups of patients was tested by independent t-test, Mann-Whitney U test and ANOVA for continuous variables, and Fisher exact test and ML chi-square test for categorical variables. The significance value was set at a p-level of lower than 0.05.

Results

The group of patients consisted of 21 people with DM1 and 49 with DM2 (Table 1). The mean age of these patients was 52 years (23–67). A significant age difference between the groups emerged immediately: the average age in the DM1 subgroup was about 20 years lower than that in the DM2 subgroup (36 vs. 56 years), but disease duration was nearly the same for both (14.6 vs. 16.0 years) and disability in both groups, as indicated by 6mWT and MRC sum score, was identical (Table 1).

Long-term muscle pain was disclosed in 57% of DM1 subjects and 55% of DM2 sufferers. The questionnaires used in this study identify pain in the previous 24 hours and in the previous week. Our own experience indicated that all patients examined in this study had suffered from pain for years. Patients were therefore asked additionally to identify ‘long-term pain’ as pain that had been present for longer than a year. Pain at the actual time of examination was reported by 52% of patients with DM1 and by 59% of patients with DM2. Its intensity, expressed on the VAS scale, was almost identical in the two groups (32.9mm in DM1 and 28.5mm in DM2). A brief evaluation of the pain in terms of the BPI questionnaire also revealed negligible differences in the intensity of pain (on a scale from 1 to 10, the DM1 average was 2.8, with DM2 at 2.7). In terms of pain descriptors, a significant difference was found only in “gnawing” pain, reported by patients with DM2 at a frequency of 20%, whereas DM1 patients made no reference to this type of discomfort at all. Most

Table 1: Sex, age distribution, and descriptors of disability (6mWT, MRC sum score).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Overall (N=70)</th>
<th>DM1 (N=21)</th>
<th>DM2 (N=49)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>22 (31.4%)</td>
<td>11 (52.4%)</td>
<td>11 (22.4%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Female</td>
<td>48 (68.6%)</td>
<td>10 (47.6%)</td>
<td>38 (77.6%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52.3 (23.6-67.3)</td>
<td>36.6 (18.4-60.3)</td>
<td>56.0 (25.2-69.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>MRC sum score</td>
<td>153.1 (110.8-170.0)</td>
<td>148.0 (119.5-169.0)</td>
<td>153.5 (108.8-170.0)</td>
<td>0.481</td>
</tr>
<tr>
<td>6-minute walk test</td>
<td>382.5 (90.0-615.0)</td>
<td>347.5 (85.0-605.0)</td>
<td>392.5 (115.0-615.0)</td>
<td>0.444</td>
</tr>
</tbody>
</table>

1The variables are described in terms of absolute and relative frequencies; statistical testing by Fisher’s exact test.
2The variable is described by themedian (5%–95% percentile). Statistical testing by Mann-Whitney U test.

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**Table 2: Short-form McGill pain questionnaire (SF-MPQ): comparison between DM1 and DM2.**

<table>
<thead>
<tr>
<th>Overall (N=70)</th>
<th>DM1 (N=21)</th>
<th>DM2 (N=49)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of pain in the previous week&lt;sup&gt;1&lt;/sup&gt;</td>
<td>29.8 (±29.0)</td>
<td>32.9 (±30.5)</td>
<td>28.5 (±28.6)</td>
</tr>
<tr>
<td>Pain quality&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Typ bolesti&lt;sup&gt;2&lt;/sup&gt; (žádná vs. jakákoli marbolesti) - SF-MPQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain present</td>
<td>40(57.1%)</td>
<td>11(52.4%)</td>
<td>29(59.2%)</td>
</tr>
<tr>
<td>Throbbing</td>
<td>21(30.0%)</td>
<td>7(33.3%)</td>
<td>14(28.6%)</td>
</tr>
<tr>
<td>Shooting</td>
<td>19(27.1%)</td>
<td>5(23.8%)</td>
<td>14(28.6%)</td>
</tr>
<tr>
<td>Stabbing</td>
<td>15(21.4%)</td>
<td>4(19.0%)</td>
<td>11(22.4%)</td>
</tr>
<tr>
<td>Sharp</td>
<td>13(18.6%)</td>
<td>4(19.0%)</td>
<td>9(18.4%)</td>
</tr>
<tr>
<td>Cramping</td>
<td>25(35.7%)</td>
<td>11(52.4%)</td>
<td>14(28.6%)</td>
</tr>
<tr>
<td>Gnawing</td>
<td>10(14.3%)</td>
<td>0(0.0%)</td>
<td>10(20.4%)</td>
</tr>
<tr>
<td>Hot/burning</td>
<td>10(14.3%)</td>
<td>2(9.5%)</td>
<td>8(16.3%)</td>
</tr>
<tr>
<td>Aching</td>
<td>34(48.6%)</td>
<td>12(57.1%)</td>
<td>22(44.9%)</td>
</tr>
<tr>
<td>Splinting</td>
<td>6(8.6%)</td>
<td>0(0.0%)</td>
<td>6(12.2%)</td>
</tr>
<tr>
<td>Tiring/exhausting</td>
<td>34(48.6%)</td>
<td>10(47.6%)</td>
<td>24(49.0%)</td>
</tr>
<tr>
<td>Squeaking</td>
<td>12(17.1%)</td>
<td>6(28.6%)</td>
<td>6(12.2%)</td>
</tr>
<tr>
<td>Fearful</td>
<td>8(11.4%)</td>
<td>3(14.3%)</td>
<td>5(10.2%)</td>
</tr>
<tr>
<td>Punishing/cruel</td>
<td>5(71%)</td>
<td>0(0.0%)</td>
<td>6(12.2%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>The variables are described in terms of average (± SD); statistical testing by unpaired t-test.

<sup>2</sup>Pain quality is described as the absolute and relative frequency representation of any degree of pain (moderate to severe pain); statistical testing by Fisher’s exact test.

**Table 3: Brief pain inventory questionnaire (BPI): comparison between DM1 and DM2.**

**Table 4: Quality of life questionnaire (SF-36): comparison between DM1 and DM2.**

**Table 5: Quality of life in relation to current pain (SF-36).**

**Table 6: Relation between myotonia and pain in DM.**

**Table 7: Relation between myotonia and pain in DM1.**

often reported by patients in both groups were "aching" and "tiring/exhausting" pains, with a prevalence of 49%. The least frequent pains were "splitting" (9%) and "punishing/cruel" (7%) pains (Table 2).

The presence of muscle pain restricts the lives of patients in normal work, general activity, and mobility; furthermore pain affects the mood or sleep of patients (as rated by BPI questionnaire). However, BPI showed the same degree of pain interference in the normal activities in both groups of DM patients (Table 3). SF-36 also showed that interference with quality of life was similar in the two groups concerning physical function, role - physical or bodily pain (not similar in general health or vitality) (Table 4), but patients with pain reported worse quality of life in all this items (Table 5).

Myotonia was reported by 83% of our patients (90% in DM1, 80% in DM2), of pronounced intensity in only 19% of them, largely in patients with DM1 (52%). Overall, the frequency of pain without the presence of myotonia was 42%, and 60% in the presence of myotonia (Table 6). Furthermore, comparison of the pain and myotonia in DM1 and DM2 separately revealed no significant difference in the frequency of pain between groups with and without myotonia (Table 7). Finally, no significant difference emerged in the frequency and intensity of pain between patients with myotonia of moderate intensity and those with pronounced intensity.

**Discussion**

A major study performed in Finland involving a group of 93 patients with DM2 also examined the frequency of muscle pain [31]. It showed current pain in 54% of patients with DM2, while their lifetime prevalence of pain was 76%. This incidence of current pain is almost identical with that of the DM2 patients in our study, (59%), and further with DM1 (52%) as well. Lifetime pain frequency among our patients was reported at 20% lower than in the Finnish study. The results of a Finnish postal survey indicated that the prevalence of “any” chronic pain within a large population sample was 35% [32]. Comparison confirms that pain among patients with DM is more
frequent than in the general population and also that pain among patients with DM2 is more frequent than in other chronic non-inflammatory muscle diseases [17].

To date, only a few studies have focused on the detection of pain in patients with myotonic dystrophy, and then usually in DM2 [17,31]. No extensive study has yet been published that compares frequency of pain in the two types of myotonic dystrophy. However, it has been observed that patients with DM1 had less pain than patients with DM2 [33]. Pain has also been reported as first symptom in 11.1% of DM2 patients and 3.0% of DM1 patients [20].

Chronic pain has been reported by 73% of people suffering from neuromuscular disease [14]. Abresch et al. [15] also found significantly greater frequency and severity of pain reported in slowly progressive neuromuscular diseases (859 participants) than levels of pain reported by the general population; the pain in slowly progressive neuromuscular diseases was comparable to that described by subjects with osteoarthritis and chronic low back pain. Other studies have reported similar results for the occurrence of pain in patients with myotonic dystrophy type 1 and 59% of patients with type 2. The frequency of muscle pain in our patients with DM is consistent with the literature. We found no significant differences between two groups of patients with DM in pain intensity or descriptors of pain. No significant association between pain and the presence of myotonia was observed in our center.

The pain descriptors employed by the short-form McGill pain questionnaire, such as hot/burning, aching, heavy, tender, and tiring/exhausting raise the possibility that the pain in the DM patients examined might be of neuropathic origin. It follows that the question of whether pain reports may be biased by the most frequent sources of neuropathic pain – diabetes and diabetic neuropathy – is worth addressing. In our DM population, the presence of diabetes mellitus was 19% (DM1) and 14% (DM2), obviously higher than that in the general population. We cannot confirm any relationship between diabetes and pain in our patients with DM. Diabetes mellitus was non-significantly more frequent in patients with pain than in those without pain in DM1 (25% vs. 11%; p 0.411; statistical testing by Chi-square test of maximum likelihood) and nearly the same in DM2 (15% vs. 14%; p 0.907; statistical testing by Chi-square test of maximum likelihood).

Myotonia is one of the key symptoms of myotonic dystrophy. In the Suokas et al. study [31], patients with pain suffered a greater intensity of muscle stiffness than patients without pain (on a numerical scale of 0 to 10, an average of 5.9 in patients with pain and 3.4 in patients without reported pain, p <0.001). In contrast to this result, our study shows no significant difference in the frequency of pain with respect to the presence of myotonia. Other summary results show that patients with DM1 had more significant myotonia and less pain than patients with DM2 (who reported greater pain not related to myotonia) [9,31]. Although these results do not correlate with our finding of a similar occurrence of pain in the two groups of patients with DM, they confirm our finding of no association between pain and the presence of myotonia.

Myotonic dystrophy negatively influences quality of life [36-39]. The presence of pain also has a profound influence on the quality of life. The Suokas et al. study [31] found a lower quality of life in DM2 patients who reported pain. Some patients report that muscular pain is the most limiting symptom of the disease [17]. The patients in our study also experienced impaired quality of life, and those with pain reported worse quality of life than those without it. Pain tends to limit patients in normal work, general activity and mobility (in terms of the items in the BPI questionnaire). However, muscle weakness due to myotonic dystrophy indisputably makes a contribution to these restrictions as well.

That the reported frequency of pain in patients with DM1 and DM2 was surprisingly similar might be a result of questions about pain being prioritized in DM2 patients. DM1 patients with more disabilities usually complain less of pain, because it is not in the foreground of the disease, unlike patients with DM2.

**Limitation of the Study**

It must be taken into consideration that this study is rendered weaker by the smaller cohort of patients with DM1 available to compare with DM2 patients, although we have included all patients being observed in our center. There is a higher number of DM2 patients in comparison with DM1 patients in the Czech Republic. For example, in February 2014, the ratio of DM1/DM2 patients in the registry was 114/171. It suggests that DM type 2 may be as common as type 1, or even more frequent in Czech Republic. However despite these limitations, this is one of the few studies to concentrate upon pain in myotonic dystrophy and one of the first comparatively larger studies to compare the frequency of pain in subtypes of DM.

Testing of myotonia was performed by one of the authors (OP) as it is described in the method section. It can be admitted, that myotonia assessment is quite subjective, so it can influence obtained result of frequency and intensity of myotonia in our patients.

Questionnaires (SF-MPQ, BPI, SF-36) have been translated and linguistically validated to the Czech language and are widely used.

Association between pain and quality of life in our study showed that patients with pain have worse quality of life. This correlation is an important clue for future research, because pain needs to be excluded in multiple linear regression analysis as a confounding variable.

**Conclusion**

The frequency of long-term muscle pain was 57% in patients with myotonic dystrophy type 1 and 55% among those with type 2. Presence of pain at examination was reported by 52% of patients with myotonic dystrophy type 1 and 59% of patients with type 2. The total frequency of muscle pain in our patients with DM is consistent with the literature. We found no significant differences between two groups of patients with DM in pain intensity or descriptors of pain. No significant association between pain and the presence of myotonia was found in our patients with myotonic dystrophy.

**References**