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SPECTRUM OF SYSTEMIC DISORDERS IN MYOTONIC DYSTROPHY

Thesis in the field of Neuroscience

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Abstract

Background: Our goal was to identify the spectrum, severity, and frequency of systemic disorders in patients with myotonic dystrophy type 1 (MD1) and myotonic dystrophy type 2 (MD2).

Methods: The national registry of muscular dystrophies exists in the Czech Republic. Using questionnaires incorporated into the registry we monitored the various systemic symptoms of the disease. From the registry, we identified frequently observed symptoms in patients with myotonic dystrophy that was less reported in the literature. Based on the information obtained we focused mainly on identifying the fertility impairment in women, the character of pain, and myotonia assessment.

Results: The MD1 females show a significant decrease of AMH values (anti-Müllerian hormone; a measure of ovarian reserve) compared with age-matched healthy controls. AMH levels were similar between females with MD2 and controls. The frequency of long-term muscle pain seems to be similar in both types of myotonic dystrophy and its frequency is about 55%. Also, the pain intensity is almost identical in both MD types. The PainDETECT questionnaire showed the presence of a neuropathic component of pain in more than half of the MD2 patients examined. QST (Quantitative Sensory Testing) has shown frequent occurrences of thermal and algic sensory abnormalities in MD2 patients. All MD1 patients and half of the MD2 patients exceeded the upper limit of normal relaxation time after voluntary contraction (which indicates the myotonia) using a commercially available dynamometer.

Conclusions: We suggest decreased ovarian reserve in women with MD1, but not in MD2. Further, we found no significant differences in the frequency, quality, and severity of pain between the different types of the disease. The pain descriptors and sensitivity profile support the hypothesis that pain in MD2 is also likely to have a neuropathic component. A commercially available dynamometer provides a valid and reliable quantitative measure of grip myotonia suitable as part of routine examinations.

Keywords: myotonic dystrophy, pain, neuropathic pain, fertility, ovarian reserve, myotonia

Abstrakt

Úvod: Naším cílem bylo identifikovat spektrum, tíži a frekvenci systémových poruch u pacientů s myotonickou dystrofií typu 1 (MD1) a myotonickou dystrofií typu 2 (MD2).
Metody: V České republice existuje národní registr svalových dystrofií. Pomocí dotazníků začleněných do registru jsme sledovali různé systémové příznaky onemocnění. Pomoci registru jsme následně u pacientů myotonickou dystrofií identifikovali příznaky, které byly v literatuře v souvislosti s myotonickou dystrofii uváděny méně často. Na základě získaných informací jsme se zaměřili zejména na identifikaci poškození plodnosti žen, charakter bolesti a hodnocení myotonie.
Výsledky: Ženy s MD1 vykazují významný pokles hodnot AMH (anti-Müllerian hormon; míra ovariální rezervy) ve srovnání se zdravými kontrolami odpovídajícího věku. Hladiny AMH byly podobné mezi ženami s MD2 a kontrolami. Frekvence dlouhodobé bolesti svalů se zdá být u obou typů myotonické dystrofie podobná a její frekvence je přibližně 55%. Intenzita bolesti je také téměř identická u obou typů MD. Dotazník PainDETECT ukázal přítomnost neuropatické složky bolesti u více než poloviny vyšetřovaných pacientů s MD2. QST (Quantitative Sensory Testing) prokázalo častý výskyt tepelných a algických senzorických abnormalit u MD2 pacientů. Použitím komerčně dostupného dynamometru všichni pacienti s MD1 a polovina pacientů s MD2 překročili horní hranici normální doby relaxace po provedené kontrakci (což indikuje myotonii).
Závěr: Předpokládáme sníženou ovariální rezervu u žen s MD1, ale nikoliv u MD2. Dále jsme nezjistili žádné významné rozdíly ve frekvenci, druhu a míře bolesti mezi oběma typy onemocnění. Deskriptory bolesti a profil citlivosti podporují hypotézu, že bolest u pacientů s MD2 pravděpodobně bude mít také neuropatickou složku. Komerčně dostupný dynamometr poskytuje spolehlivé kvantitativní měřítko testování myotonie vhodné jako součást rutinních vyšetření.

Klíčová slova: myotonická dystrofie, bolest, neuropatická bolest, plodnost, ovariální rezerva, myotonie

I declare that I have prepared the thesis independently under the guidance of MUDr. Stanislav Voháňka, CSc., MBA using sources listed in the bibliography.

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Content

1. Introduction

Myotonic dystrophy (MD) 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 several organ systems. The disease is divided into forms: type 1 (MD1) and type 2 (MD2). The "classic" type of myotonic dystrophy first described Steinert and colleagues in 1909 and it was called Steinert's disease (now MD1). Myotonic dystrophy type 2 was described much later, in 1994, as a new dominant disorder with lacking the gene defect responsible for Steinert's disease and was called Proximal myotonic myopathy (PROMM) or proximal myotonic dystrophy (PDM) in Europe [1–3], or myotonic dystrophy type 2 in the United States (current designation) [1]. Thus, these are two different diseases that share several features and pathogenetic mechanisms with similar diagnostic approaches and therapeutic consequences.

2. Prevalence

The prevalence of the disease (combined for both MD types) is estimated to be 12.5 per 100,000 inhabitants (1/8,000) [4]. Although worldwide estimates of prevalence vary widely between different geographical and background-specific populations, usually between 0.5 and 18.1 per 100,000 [5–8]. MD1 occurs worldwide with a significantly higher incidence in some regions, like Quebec (158 cases per 100,000 population) or Basque Country (26.5 cases per 100,000 population) [9,10]. The prevalence is thus especially high in the less densely populated areas or regions [8]. MD2 is more frequent in the Central European region and Northern Europe, with a high prevalence of MD2 mutations reported in the population of Finland: 54.6 per 100,000 inhabitants [5]. The authors of this study suggest that MD2 patients are under-diagnosed because the symptoms of the disease frequently occur in the elderly population that making the diagnosis more complicated [5]. Therefore, we can suppose that the real prevalence of MD2 is significantly higher than reported. In the Czech Republic, like in other countries of central Europe, the prevalence of MD2 is higher than MD1 according to data from the register [11].

For many countries, myotonic dystrophy represents the most common inherited muscle disorder in adulthood, but regional variations exist in the prevalence and incidence of each type. In most of the population, type 1 MD appears to be more common than type 2 [12]. However, certain studies suggest that type 2 may be as common as type 1, and perhaps even more frequent, in particular in northern and Central European countries such as Finland, Germany, and Czech Republic [5,11–13].

3. Genetics

The disease has an autosomal dominant pattern of inheritance with two genetically distinct types of disease. 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 dystrophia myotonica-protein kinase (*DMPK*) gene on chromosome 19q13.3 (MD1) and expanded and unstable tetranucleotide (CCTG) repeat in nucleic acid-binding protein (*CNBP*) gene on chromosome 3q21.3 (MD2, previous known as the zinc finger 9 (*ZNF9*) gene) [14–16]. In both cases, the gene including the abnormal repeat expansion is transcribed into RNA (ribonucleic acid) 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, which affects a lot of cells and organs of the human body, giving rise to the extremely heterogeneous phenotype with multisystemic involvement typical for the MD [17]. The gene defect responsible for MD1 was found in 1992 [14,15] and later in 2001 for MD2 [16].

4. Molecular pathomechanism

The fact that two repeat sequences located in different genes cause so similar disease features suggests the same (or similar) pathogenic mechanism [18]. As mentioned above, the expansion mutations (CTG/CCTG) are transcribed and these mutant RNAs with repeat expansions accumulate in the cell nuclei as foci, called ribonuclear inclusion [19–21]. This gain-of-function RNA mechanism is responsible for the pathologic features common to both disorders [20]. The expanded transcripts (CUG/CCUG) form hairpins (imperfect double-stranded structure), which lead to deregulation of important RNA-binding proteins, as muscleblind–like protein 1 – 3 (MBNL1 – 3), CUGBP/Elav-like family member 1 (CELF1), or CUG-binding protein 1 (CUGBP1) [18,21–23]. The result is the decrease of MBNL1 and increase of CELF1 or CUGBP1 activity that lead to misregulation of alternative splicing other genes and other changes of the muscle transcriptome, which plays a main role in the development of MD symptoms [18,22,24]. It was identified more than 30 genes whose splicing is affected [4]. This hypothesis of a "spliceopathy" is also strengthened by recent data demonstrated that MBNL1-containing foci in MD2 cells also sequester snRNPs and hnRNPs, the splicing factors involved in the early phases of transcript processing [21,23,24]. This mis-splicing tends to revert the splicing pattern to comprise many embryonic splice variants [25]. Although the spliceopathy may not fully explain the multisystemic disease spectrum of MD,

the typical symptoms of the disease as myotonia, insulin resistance, and cardiac problems are correlated with the disruption of the alternative splicing of the muscle chloride channel ClC-1 (chloride voltage-gated channel 1, CLCN1), sodium channel SCN4A (sodium channel type 4 subunit alpha), the insulin receptor, or the cardiac troponin T [26–30]. The mechanism responsible for muscle weakness and wasting is more complex with multiple pathogenic ways of altered transcription, translation, and cell signaling [18]. Pathological splicing of the bridging integrator-1 (BIN1) pre-mRNA in skeletal muscle plays a role in the pathogenesis of muscle weakness, and it is more evident in the muscles of MD1 patients than in MD2 patients [31]. Abnormal splicing of some sarcomeric proteins such as LDB3 (LIM domain-binding protein 3), MYOM1 (myomesin 1), and MYH14 (Myosin Heavy Chain 14) has also been described [32–35]. Alternative splicing of the calcium channel subunit CAV1.1 (CACNA1S) is also involved in the pathogenesis of muscle weakness [36]. It has been also described microRNAs dysregulations by MBNL1 in the pathogenesis of MD contributing to alteration of skeletal muscle and heart tissue [37–39]. There are phenotypic differences between the two MD forms. The fact that MD1 and MD2 have clinical differences indicates that additional factors are contributing to the disease pathomechanism besides the misregulation of alternative splicing. The reason may be the changes in the expression of neighboring genes of DMPK and CNBP or evidence that abnormal ZNF9 levels in MD2 may be altered on multiple levels and make the differences between MD1 and MD2 [18,40,41]. Thus it is possible that apart from the RNA toxicity the respective gene loci are contributing in different ways to the phenotype.

5. Genotype-phenotype correlations

For MD1, there is a correlation between the expansion of CTG-repeats and the onset of symptoms as well as the severity of the disease, ranging from mild to severe [42,43]. 5 to 37 CTG-repeats are physiologic and occur in healthy individuals [18]. An expansion of CTG-repeats between 38 and 49 reflects the pre-mutation phenotype typically without clinical symptoms, but with the risk of having children with larger, pathologically expanded repeats [18,44]. An expansion between 50–100 CTG-repeats causes a mild phenotype of disease or could be asymptomatic into old age [45]. A classic “adult-onset” MD1 with mild to severe phenotype has an expansion of 50–1,000 CTG-repeats [18]. There is also a childhood/juvenile phenotype with early-onset disease and typically has >800 CTG-repeats [46]. In the case of MD1, there is the most severe congenital form of the disease with usually >1,000 CTG-repeats [46]. These correlations between phenotype and number of repetitions in MD1 are

shown in table 1. It is important to know, that phenotypes and CTG-repeat sizes do not show a strict relationship and phenotypes may overlap [47,48]. It was also found that CTG-repeat size correlates more significantly with the age of onset and disease severity below 400 CTG repeats [49]. Another finding is that the repeat length can vary between different tissues significantly, so the correlation between CTG-repeat size and the severity of the disease can be observed in the blood (in leukocytes) but not in other organs like is a muscle, where the repeat lengths are shown to be larger with no correlation between the repeat size and the degree of weakness [50,51]. Permanent somatic instability with variation in different tissue and cell types creates inter-tissue and inter-cell variability in the number of repetitions causing somatic mosaicism [51,52]. Moreover, it seems that gene defects in MD are dynamic, and repeat size appears to increase over time in the same individual [53]. This complicates a prediction of the clinical development of patients as the repeat length is usually measured in DNA (deoxyribonucleic acid) gained from the blood.

In the congenital form of MD1, these large expansions are almost always caused by maternal transmission, but although it may be unusual, the possibility of the paternal transmission of congenital form is also known and should be mentioned when counseling families with MD [42,54,55]. It is interesting about paternal transmission, described in one study, that all fathers whose status was known had small repeat sizes and/or were asymptomatic at the time of their child's birth [54].

In the case of MD1, we can observe the anticipation phenomenon, when CTG-repeats will expand in every following generation with an earlier onset of disease and a more severe phenotype in the next generations [48]. The cause of anticipation is the instability of triplets in germ cells [51]. It is significantly higher in maternal alleles (children with the congenital form of MD1 are almost exclusively born to affected mothers), on the contrary, instability in male alleles can lead rarely to shortening of the expanded segment [51,56,57]. Furthermore, the repeat instability leads to premature aging of almost all organs, so MD1 may be counted among the progeroid diseases [25,58].

The size of the CCTG repeat in normal individuals is below 30 repeats [59]. In MD2 the smallest reported mutations were found between 55-75 CCTG (however, it is uncertain whether there was a significantly greater degree of expansion in some tissues due to mosaicism) [16,59], usually, it is around 5,000 repetitions, and the largest expansions have been reported to be up about 11,000 repeats [16]. As well as in MD1, we can find the premutation extent of repetition in MD2, repetition between 23–33 shows significant instability in the European population [5,59]. In MD2 we don´t observe the correlation

between the expansion of CCTG-repeats and disease severity. There is also a missing of a congenital form and we don´t note the anticipation phenomenon [60].

Both types of MD are monoallelic dominant diseases, one mutated allele is enough for the full development of the disease. In general, the homozygous state of expansive autosomal dominant gene mutations does not change (not getting worse) the phenotype of the disease compared to the heterozygous state. It is very rare in MD and has so far been described in only a small number of patients of both types of disease, and the clinical character and course of disease did not differ from carriers of heterozygous monoallelic mutations [61–63].

6. Clinical features

Clinically, this multisystemic disorder is characterized by muscular and high variability of extramuscular symptoms.

The MD1 recognizes four main forms: congenital, an early-onset, adult-onset, and late-onset/asymptomatic.

The congenital form of MD1 is the most severe form of the disease with symptoms before birth as polyhydramnios and reduced fetal movement [64,65]. Children may be born as premature infants and at birth or in the first days after delivery the typical symptoms are hypotonia, severe generalized weakness, facial weakness with a weak cry and the inability to suck, hyporeflexia, contractures, or arthrogryposis [65]. One of the features of affected infants is facial dysmorphia, like carp mouth or "fish-shaped" upper lip, an inverted V-shaped upper lip which is characteristic of severe facial weakness, then ptosis, long neck, and face or temporal muscle atrophy [18]. Respiratory insufficiency with respiratory failure and cardiorespiratory complications dramatically reduced the survival of newborns with a mortality rate of 30–40% [66]. Children reach their motor skills usually with some delay, but almost all children can walk. Besides muscular symptoms, cognitive impairment, mental retardation, learning disability, apathy, autism, impaired attention, anxiety, and depression are common manifestations in the congenital form of MD1 [67–70]. Mental retardation and cerebral atrophy may even precede the development of muscle weakness [71]. Furthermore, other abnormalities are associated with the congenital form of MD such as hydrocephalus, inguinal or hiatus hernia, undescended testis, congenital dislocation of the hip and heart defect, congenital cataract, or cleft lip [72,73].

The early-onset form of MD1 includes childhood and juvenile form and consists of a spectrum of symptoms of both the congenital and the adult phenotypes. In childhood-onset form, the first clinical symptoms may manifest at age 1–10 years and age 10–20 for juvenile-

onset form [44]. Some symptoms like learning difficulties may become before muscular symptoms [70]. For childhood or juvenile type of MD1 are not typical symptoms like prenatal abnormalities or muscular symptoms right after delivery. Mild facial weakness or some facial dysmorphia may occur [44]. The main symptoms in the childhood-onset form are speech and learning difficulties because of mental handicap and low intelligence quotient (IQ) [70]. A study on MD1 patients with childhood form showed that the full-scale IQ was significantly decreased and additional psychiatric symptoms such as anxiety disorder, mood disorder, and attention-deficit-hyperactivity disorder were frequent [70]. The typical muscular symptoms like distal weakness and clinical myotonia may be presented in adolescence. The early conduction abnormalities are frequently described in this form and annual electrocardiograms and electrophysiological studies should be a part of routine management [18].

The core features of classic adult-onset MD1 are described below. Typical muscle and extramuscular involvement described in this work in MD1 patients are related to the adult-onset form of the disease. The first symptoms of classic MD1 usually arise between the ages of 20 and 30.

Mildly affected patients with late-onset form (with a low number of CTG repeats) and only minimally symptoms of the disease may have their diagnosis delayed until they are around 40 years old (the age of onset ranges between 20 and 70 years) [45]. Patients may have only limited symptoms like mild myotonia, cataracts, or diabetes mellitus only, or even they are asymptomatic with no evidence of myotonia when using EMG [45].

In MD2 there are no distinct clinical subgroups and congenital or early-onset form does not exist [53]. The clinical onset of MD2 typically occurs later than MD1, around the third to fourth decade. Many patients may be unrecognized for several years due to only mild or unspecific clinical symptoms like myalgia [74]. Patients with onset of muscle weakness at old age may not be indicated for neuromuscular investigations due to generally expected weakness in elderly patients. Consequently, the majority of MD2 patients could be undiagnosed because of mild, unspecific, or late onset of symptoms. Some MD2 patients could be asymptomatic even until old age and they are detected (genetically) after diagnosing the disease in another family member. MD2 has variable manifestations, such as early-onset cataracts, mild myotonia, thigh muscle stiffness, and muscle pain, as well as weakness.

Because of comorbidities, such as cardiac and pulmonary complications, life expectancy usually in patients with classic MD1 phenotype is reduced [47]. Mortality and morbidity in MD thus significantly depend on these systemic involvements and requires early diagnosis and treatment of these comorbidities [75]. In MD1 patients the life expectancy is greatly

reduced, particularly in those with early onset of the disease and proximal muscular involvement [7]. The high mortality reflects the frequent respiratory diseases, cardiovascular diseases, neoplasms, and sudden deaths presumably from cardiac arrhythmias [7].

Both types of disease have many similar symptoms and findings, but some features allow clinical distinction between MD1 and MD2 [12,18]. This is shown in table 2.

6.1. Muscle symptoms

The typical MD1 phenotype is characterized by a distinctive combination of muscular symptoms, such as facial weakness with ptosis, grip myotonia, and distal muscle weakness with muscular atrophy. Clinical symptoms of MD2 patients have large phenotypic variability from asymptomatic patients to severe muscular weakness.

The changes in muscles of patients with both types generally lead to muscle atrophy. Muscle atrophy is mostly present in MD1 and is located especially in the face, distal hands, and legs. In MD2 muscular atrophy is usually absent. In contrast to muscular atrophy, some muscles enlarge, because muscle tissue is replaced by fat and connective tissue [76]. The enlargement often develops in MD2 patients, is most notably in calf muscles (gastrocnemius), and is called calf pseudohypertrophy, or "false enlargement". Pseudohypertrophy in MD2 patients can also occur in the muscles of the thighs.

6.1.1. Muscle weakness

The disorder manifests as progressive muscle weakness. Muscle weakness is the main and one of the most frequently reported symptoms in MD1 and MD2 [48,77].

Patients with MD1 have predominantly distal muscle weakness with muscular atrophy. Distal weakness mainly involves finger flexors, wrist flexors, and foot extensors. This muscle weakness leads to difficulty with performing tasks requiring fine dexterity of the hands. Distal foot weakness with foot drop frequently leads to repeated falls and injuries [78]. Over time, muscle weakness progress, and patients may have a slow proximal progression of muscle weakness. Sometimes proximal muscle weakness can occur late in the disease course. Nevertheless, in many patients, proximal strength remains preserved despite significant distal weakness. Weakness and atrophy of facial muscles and ptosis cause the typical “myopathic face” of MD1 patients. This is a prominent feature of type 1 myotonic dystrophy, and this typical facial appearance may make an impression of a tired, sad, or emotionless patient [79]. Severe weakness of orbicularis oculi muscles causes ptosis and insufficient eyelid closure with the risk of recurrent conjunctivitis [12]. The weakness of oropharyngeal muscles causes

swallowing difficulties. Also, speech can be nasal and slurred due to the weakness of facial and oropharyngeal muscles [18]. The neck flexors are also commonly involved. The atrophying of temporal muscle and balding of the forehead completes the overall picture of a patient with MD1 [18].

Muscle weakness in MD2 is typically proximal and axial, affecting more consistently the neck flexors, hip flexors, and hip extensors [53,77]. The long flexors of the finger muscles could be also affected in MD2 [18], but it is less affected than proximal muscles. Early in the onset of MD2, only mild weakness of hip or thigh flexion and extension could be present. Subsequently, the weakness usually slowly progresses. This predominantly proximal muscular involvement has been documented also by MRI studies that showed an early degeneration of the erector spinae and gluteus maximus muscles [80]. For MD2 patients is not typical facial muscle involvement like in MD1.

Respiratory muscle weakness is frequent for MD1 patients but rarely occurs in MD2. Weak or inefficient respiratory muscles might not permit a normal ventilatory response to a hypoxic stimulus. It may leads in MD1 to recurrent pneumonia and chronic respiratory failure with the requiring of non-invasive ventilation [81]. Patients with advanced respiratory muscle weakness have an increased risk of post-operative complications such as acute respiratory failure and aspiration pneumonia [82]. Furthermore, the involvement of the respiratory muscles can predispose to breathing and oxygenation changes during sleep. Besides respiratory muscle weakness, hypoventilation may be also centrally mediated. When sleep and breathing in patients with myotonic dystrophy type 1 were compared with those in patients with nonmyotonic respiratory muscle weakness and control subjects, periods of hypoventilation and apneas occurred in those with myotonic dystrophy at higher incidences than in nonmyotonic patients who had the same degree of respiratory muscle weakness [83]. Other authors used transcortical and cervical magnetic stimulation in conjunction with phrenic nerve recordings, which demonstrated that more than 20% of patients with myotonic dystrophy have impaired central respiratory drive [84]. Also, the finding of neuronal loss in the dorsal central, ventral central, and subtrigeminal medullary nuclei in patients who exhibit alveolar hypoventilation, and the severe neuronal loss and gliosis in the tegmentum of the brainstem may support a central abnormality of breathing impairments in myotonic dystrophy type 1 [85,86]. Observations of decreased ventilatory response to hypoxic and hypercapnic stimuli [87] and extreme sensitivity to sedative drugs [88] could further support a central origin of the breathing impairments in myotonic dystrophy. These all findings add to evidence that respiratory muscle weakness alone does not account for abnormal breathing in patients

with myotonic dystrophy. Besides respiratory muscle weakness and the central origin of the breathing impairments, the obstructive changes and disorders may also contribute to hypoventilation. In MD1 patients the development of craniofacial structures could be impaired, as a result of muscle weakness, and patients experience more vertical facial growth, they have more narrowed maxillary arches and deeper palatal depths, which altogether can contribute to the development of obstructive respiratory problems [89].

6.1.2. Myotonia

Myotonia is defined as delayed relaxation of skeletal muscle after voluntary muscle contraction or external mechanical stimulation (e.g. percussion) and thus reflects a state of muscle fiber hyperexcitability. Pathophysiological, myotonia is caused by permanent depolarization of sarcolemma due to impaired chloride or sodium ion channels of the muscle membrane. Although the definitive molecular basis for myotonia is unclear, it has been suggested that myotonia in myotonic dystrophy is caused by alterations in the expression of both chloride (CIC-1) and potassium (SK3) channels. Aberrant pre-messenger RNA splicing of the chloride channel ClC-1 due to misregulated MBNL1 and CUGBP1 results in loss of CIC-1 channel protein from the sarcolemma and this reduces transmembrane chloride conductance causing membrane hyperexcitability and myotonia [18,27]. Next to chloride channel dysfunction it appears to be the occurrence of increased expression of apamin-sensitive small conductance calcium-activated potassium channel (SK3) in MD1 skeletal muscle [90,91] that are normally well expressed in developing or denervated skeletal muscles [92]. SK3 plays an important role in regulating membrane hyperpolarization in relationship to the intracellular calcium concentration and thus increased level of SK3 channels can contribute to myotonia [92].

Myotonia can be detected on electromyography (EMG) as spontaneous activity of motor units with a characteristic increase and decrease of frequency and amplitude of the signal (Figure 1). These "myotonic discharges" create on EMG a unique sound similar to a motorcycle engine or chainsaw [93]. This activity on EMG could be observed also in clinically unaffected muscles [94]. Electrical myotonia can also be seen rarely in other circumstances: with certain drugs (cholesterol-lowering agents, cyclosporine, or colchicine, among others), in inflammatory myopathies, Pompe disease, hypothyroidism, myotubular myopathy, and chronic denervation [95,96].

Myotonia typically improves after repetitive movements (warm-up phenomenon) and it is usually observed in grip myotonia. Myotonia is usually exacerbated by cold.

In adult-onset MD1 patients myotonia is a frequent symptom, nearly as muscle weakness. The most frequent myotonia affects the fingers (grip myotonia), however other muscles could be also affected including the bulbar and facial muscles, causing problems with talking, chewing, swallowing, or eyelid opening [97]. In leg muscles, myotonia may complicate walking or running. Myotonia of respiratory musculature, in addition to muscle weakness, can affect pulmonary function resulting in dyspnea. Also, percussion myotonia during the investigation is a regular feature in MD1. In some patients, myotonia can seriously interfere with activities of daily living.

In MD2 patients myotonia is often less apparent compared with patients with MD1 and is usually mild to moderate intensity with a little impact on the quality of life [97]. The clinical evidence of myotonia (grip or percussion) is observed on neurological examination only in a minority of MD2 patients. In the majority of patients, myotonia may only appear on electromyographic examination [46]. Nevertheless, we can find the occurrence of myotonia in MD2 patients in the literature about 25 and 75% [53,77,94]. This large range could be due to inconsistencies in the assessment of myotonia between a history of myotonia reported by patients and the clinical evidence of the myotonic phenomenon [12]. An even greater range of presence of myotonia is in the case of electrophysiological myotonia, which may be present in 90% of patients [53].

In some MD2 patients, we can observe severe myotonia. In these cases the additional mutations in ion channel genes CLCN1 and SCN4A should be identified, because these can act as phenotype modifiers enhancing the myotonic phenomenon in MD2 [98–100]. In MD2 patients with co-segregating of CLCN1 mutation, the severity of myotonia appears to be more evident, thus these patients could be more easily identified than patients without the modifier allele [101].

The correlation between myotonia and CTG-repeat length in MD1 patients has contradictory reports. Whereas grip strength usually correlates negatively with CTG-repeat length, this is not necessarily true for myotonia, although a statistically significant correlation was also found [102,103]. There are also contradictory reports about the correlation between grip myotonia and pain. In the Suokas et al. study [104] patients with pain suffered a greater intensity of muscle stiffness than patients without pain. Nevertheless, other studies show no association between pain and the presence of myotonia [13,105].

6.1.3. Pain

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 60% - 83% [106–112]. The intensity and frequency of pain in progressive neuromuscular diseases are significantly higher than in the general population [111]. 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 [110]. Pain is often a symptom for patients with myotonic dystrophy. It may fluctuate over time and can be influenced by exercise, palpation, and cold temperature [104,113,114]. The comparison confirms that pain among patients with MD is more frequent than in the general population and also that pain among patients with MD2 is more frequent than in other chronic non-inflammatory muscle diseases [113]. Widely it is noted that the incidence of pain is higher in MD2 patients than in MD1 [12]. Nevertheless, it could be a result of questions about pain being prioritized in MD2 patients, because MD1 patients with more disabilities usually complain less of pain, as it is not in the foreground of the disease, unlike patients with MD2. Considering, the frequency of pain in both types might be surprisingly similar.

Pain has been also reported as the first symptom of disease, namely in 11.1% of MD2 patients and 3.0% of MD1 patients, so pain is also an important indicator of the onset of MD [74]. Patients complain of various types of pain, myalgia, and cramps, most often located in the thighs, back, and proximal upper limbs [13].

Although pain is a common clinical symptom in MD, the etiology of pain is unknown and is probably to be multifactorial. It is also not clear why the pain develops in some MD patients and others do not, or why the pain often occurs at the stage of the disease when there is no clinically manifest involvement of the muscular system [74]. One of the possible hypothesis of pain in MD may be, for example, an abnormal load on the musculoskeletal system due to muscle imbalance of weak muscle groups, or due to deep muscle myotonia, when long increased deep muscle tone depletes the muscles of this group and their antagonists [12,112]. Long-term muscle contraction in myotonia can also lead to hypoperfusion, lactate accumulation, a decrease in pH, and the release of other substances that can provoke the pain, such as bradykinin, adenosine triphosphate, and hydrogen ions [115]. Muscular imbalance due to weakness may lead secondary to myofascial pain or joint pain syndromes. Changes that are directly related to the pathophysiological process of the disease in its multisystem manifestation, where the accumulation of expanded transcribed RNA damages cellular

processes and affects the RNA splicing of other genes, could also contribute to pain [116,117]. This pathophysiological process may also increase nociception. Maybe all the mentioned mechanisms are rather hypothetical and clear evidence of their importance in the pathophysiology of pain for MD is not yet available. The nature of pain in patients with MD may be very variable. Some of the pain descriptors indicate the possibility of the neuropathic component of pain in MD patients. As one of the multisystem manifestations in MD, peripheral nerve involvement has also been described [118,119].

6.2. Extramuscular symptoms

Myotonic dystrophy is a multisystem disorder witch often presents with a high variability of symptoms and multi-organ involvements, involving the cardiovascular, endocrine, central nervous, respiratory, gastrointestinal, ophthalmologic, or genitourinary systems. Some patients may have only non-specific extramuscular symptoms like fatigue or some gastrointestinal symptoms, and these varied symptoms could delay the diagnosis. As muscular weakness worsens over time, is observed relationships between organ dysfunctions and muscular impairment in MD1, and that MD1 patients with proximal weakness had a higher risk of multiple organ dysfunction [120].

It seems that multisystemic involvement in MD patients could reflect the appearance of accelerated aging [25]. Visible aging features such as cataracts, muscle weakness, and frontal baldness, but also less obvious features like cardiac arrhythmia, diabetes, or hypogammaglobulinemia suggest the hypothesis that MD could be a segmental progeroid disease [25]. In a recent study, authors compared the aging symptoms in MD to “typical” progeroid disorders which mimic physiological aging and are caused by mutations in nuclear envelope proteins, proteins involved in their processing, or DNA-repair proteins [25]. This analysis reveals many similarities of MD to progeroid syndromes linked to the nuclear envelope and had qualified MD on both clinical and molecular levels as a segmental progeroid disorder [25].

6.2.1. Cardiac Symptoms

Cardiac involvement in MD is common and it is observed that frequency and severity of cardiac involvement are much severe and frequent in MD1 than in MD2 [121,122]. Clinical manifestations of cardiac involvement have a wide spectrum even among members of the same family [123]. Patients may present symptoms such as palpitations, chest pressure/pain,

dyspnea, dizziness, fatigue, presyncope, or syncope. Regardless, cardiac conduction disturbances may progress rapidly, and result in severe bradycardia or asystole [82].

In MD1 cardiac abnormalities include the spectrum of different conditions, like arrhythmias, conduction defects, dilated cardiomyopathies, heart failure, Brugada syndrome, ischemic heart disease, or mitral valve prolapse [75,124]. Histopathologic lesions of the cardiac conduction system observed in MD1 were fibrosis, fatty infiltration, and atrophy [125]. Fibrosis and fatty infiltration were observed in the sinus node, atrioventricular node and bundle, bundle branches, and ventricular myocardium [125]. Atrophy affects prominent atrioventricular bundle and bundle branches [125]. Cardiac involvement can contribute to sudden death and the risk of sudden cardiac death in the MD1 population is found out to be 0.56% per year [125,126]. The most common cause of sudden cardiac death are bradyarrhythmias with asystole, bradycardia-induced ventricular fibrillation, ventricular tachycardia, or left ventricular systolic dysfunction [127,128].

Early and extensive involvement of the conduction system presents the major cardiac abnormality seen in MD1 [127]. Cardiac fibrosis and fatty infiltration of the heart affect the His–Purkinje system, the sino-atrial and atrioventricular nodes that cause the conduction block, ectopic activity, and re-entrant arrhythmias [127]. Atrial tachyarrhythmias (atrial tachycardia, atrial fibrillation, and atrial flutter) are the most common arrhythmias and arise probably due to regions of atrial fibrosis. Ventricular tachycardia and ventricular fibrillation due to re-entry circuits are caused by fibrotic foci, fatty infiltration, or triggered activity [126]. These changes can present as palpitations, syncope, and sudden cardiac death [126]. The meta-analysis of 1828 MD1 patients revealed the most common 1st degree AV block in 28.2%, then prolonged ventricular systole period in 22.0%, prolonged QRS interval in 19.9%, frequent premature ventricular contractions in 14.6%, atrial fibrillation/flutter in 5.0%, right bundle branch block in 4.4%, left bundle branch block in 5.7% and non-sustained ventricular tachycardia in 4.1% [126]. Arrhythmias often require the implantation of pacemakers [121,129]. The prevalence of pacemaker and cardioverter-defibrillator implantations in MD1 patients could be approximately 4 % and 1 %, respectively [126].

Structural cardiac abnormality like left ventricular hypertrophy, left ventricular dilatation, left ventricular systolic dysfunction or mitral valve prolapse was observed in MD1 with a prevalence between 14 – 20 % [130,131]. Besides the left atrial enlargement and left ventricular non-compaction/hypertrabeculation have been observed in MD1 [130,132]. These structural abnormalities lead to cardiomyopathy with cardiac dysfunction and heart failure, and typically occur in the late stages of the disease [133]. Due to the structural cardiac

abnormalities, the left ventricular dyssynchrony with increased early diastolic cavity tension can reduce the flow of blood volume into the coronary arteries and causing subendocardial ischemia even in the absence of epicardial coronary disease [134]. Moreover, the global and regional coronary reserves can be impaired, also concerning the DNA mutation size, in asymptomatic MD1 patients due to impairment of vascular smooth muscle of the heart [135].

The severity of cardiac involvement in MD1 (sudden deaths, conduction defects, left ventricular dysfunction, and supraventricular arrhythmias) could be associated with the size of CTG expansion [126,136], however, some observations exude the correlation of CTG expansion with clinical cardiac disease [137,138]. The association between cardiac conduction disturbances and age, duration of neurological disease, and male gender seem to be more consistent than with CTG repeats [126,139]. Male gender and age were positively associated with arrhythmia and conduction abnormalities [126]. Moreover, the situation is complicated that skeletal and cardiac muscle DNA expansion lengths may be longer than peripheral blood leucocyte DNA [50].

In contrast with MD1, the prevalence of cardiac involvement in MD2 is not so high but is significantly more frequent than in the control population [121,140]. Cardiac abnormalities in MD2 are reported with a variation of 17% to 36% and include conductive defects (the first-degree atrioventricular block or bundle branch block), systolic dysfunction, or supraventricular arrhythmias [121,129,140]. Also in MD2 myocardial fibrosis is related to conduction abnormalities like was described in MD1 [141]. When compared to MD1 patients, conductive defects seem to be less frequent, supraventricular arrhythmias have a similar prevalence and there is a trend towards more frequent left ventricular dysfunction in MD2 patients [140]. Although severe cardiac arrhythmias with pacemaker implantation or sudden death have been also described in some MD2 patients [121,142], this is not a common feature.

Cardiac involvement contributes significantly to the morbidity and mortality of the disease with premature death [127]. The life expectancy of patients with MD1 is reduced with a mean age at death of 53 years [7]. The cardiac origin as the cause of death is stated to be in approximately 30% of cases [7,143]. Moreover, it's dangerous, that early stages of cardiac involvement could be clinically silent.

Based on all findings the systematic cardiac investigations should be recommended in MD patients to identify patients at risk for potential major cardiac involvement. It is recommended a follow-up through 24 h Holter monitoring and echocardiography [144]. In clinical routine, usually, echocardiography is used to assess heart function as a first-line method, nevertheless,

cardiovascular magnetic resonance can early detect the subclinical myocardial involvement still in preserved left ventricular ejection fraction [141].

6.2.2. Ocular symptoms

The key feature and most frequent extramuscular manifestation of the disease is early-onset cataract observed in about 50–60% of patients, increasing with age [2,53,77,145]. Cataract could be the initial feature of the disease around in 8% of patients, however, even in 25% of MD2 patients cataract was reported to be the first symptom of the disease [53,74,146]. In many cases, even in mildly affected patients without any or minimal sign of muscular impairment, the history of cataract or cataract surgery often helps to the diagnosis of MD [145–148]. Thus the ophthalmologists can be the first physicians encountering these patients and especially in the cases of absence of other secondary causes of cataract, the ophthalmologists should refer these patients for neuromuscular evaluation. Cataracts appear identical in MD1 and MD2 and develop usually before 50 years of age [146]. In MD are commonly observed the posterior subcapsular or cortical type of cataract and lens opacities are visualized by slit-lamp eye examination [146]. In the lens cortex, fine iridescent opacities develop and later grow into a stellate cataract in the posterior subcapsular region [149]. When opacities more advanced, differentiation from other cortical cataracts become difficult [149]. When cataracts interfere with acuity, cataract removal with an intraocular lens implant is recommended. The phenomenon of recurrent posterior capsule opacification after cataract surgery is also possible and described in patients with MD [150].

Studies of global transcription performed on samples of the lens epithelium, identified in lens cells a role of mutant RNA in the activation of the innate immune response and interferon signaling pathways in MD1 and MD2 cataracts [149]. The mechanism of the pathophysiology of the cataract in MD1 could be also explained from the expansion of CTG triplets that decreases expression of the adjacent gene SIX5 whose transcripts are detected in the normal adult eye corneal epithelium and endothelium, lens epithelium, ciliary body epithelia, cellular layers of the retina and the sclera [151,152]. The authors thus hypothesized that the dysfunction of SIX5 is primarily responsible for the ophthalmic features of MD1 [151]. In the case of MD2, the cause of cataract is the "distant" toxicity of CCTG transcripts [153,154].

In MD1 patients eyelid ptosis can be severe and obstruct vision. Surgical intervention may be required, however, blepharoplasty should be deferred as long as possible preventing the need for recurrent surgeries as muscle weakness progresses. Also, other ocular symptoms are described in MD1, include sluggish (weak) pupillary response to mydriatics, the high cup-to-

disc ratio with retinal nerve fiber layer defect, external ophthalmoplegia, epiphora, pupillary light-near dissociation, retinal pigment epithelium changes, or ocular hypotony [155,156].

6.2.3. CNS Symptoms

Several findings indicate a high frequency of central nervous system (CNS) involvement in myotonic dystrophy. Pathological findings in both types of disorder consist of white matter lesions and brain atrophy, while in particular anterior temporal white matter lesions were exclusively seen in MD1 patients [157–159]. Both types of MD are thus serious white matter diseases with a prominent callosal body and limbic system affection, while white matter changes dominate the extent of grey matter changes (Figure 2) [160]. Some authors described the correlation between changes in brain white matter and cognitive impairment in MD1 [160,161]. Cognitive and psychiatric dysfunction such as reduced intelligence (low IQ), mental retardation, or behavioral disturbances are frequent symptoms in MD1, but more often may be seen in patients with congenital and early-onset forms of MD1 [69,162]. In childhood and juvenile form of MD1, we can also observe children with an autism spectrum disorder, an attention-deficit disorder with hyperactivity, and anxiety disorder [68,69,163]. For the classic adult-onset phenotype of MD1, the neuropsychological deficits are variable and recent publications show contradictory study results about the correlation of CTG-repeat size and neuropsychological deficits [67,164–166]. The study focused on personality in classic MD1 indicates deviant personality regarding temperament and character of patients [167]. Moreover, patients may have obsessive-compulsive personality, passive-aggressive personality, schizotypic traits, dependent tendencies, or mood disorders [168]. In both patient groups of MD, there is a high incidence of avoidant personality trait disorder, such as reluctance to make new friends, carry out new activities, or take personal risks [162,168].

Avoidant personality disorders are stated to be the most common symptoms of personality disorders in MD1 [169]. A lot of studies in the literature provided evidence about the presence of depressive disorders in the MD1 population. In some studies, patients presented mild depressive symptomatology or depressiveness [160,170,171], in others moderate depressive symptomatology [172–174], while some authors in MD1 patients did not find any significant difference for depression [175].

In addition, the myopathic face of MD1 patients triggers the general perception of cognitive deficiency and low educational level or may be confused with depressive symptoms [170,172]. Nevertheless, a recent study about the educational profile of a large cohort of young MD1 and MD2 patients shows rather normal general educational levels in patients with

myotonic dystrophy [79]. It is possible, that cognitive and concentration disturbances may occur later in the course of the disease in the context of a premature cognitive decline [164]. In MD2 patients mild cognitive and behavioral symptoms could be also present. The specific cognitive and behavioral profile with altered executive functions reduced attention and flexibility of thinking, and depression has been detected in these patients [159,162]. These neuropsychological disturbances in many cases may affect the ability to work and reduce the quality of life more than muscular symptoms [12]. Also, mental retardation in MD2 individuals has been reported, but these occurrences may be rather accidental [53].

It seems, that apathy is a frequent symptom in MD1 [172]. Apathy was determined to be associated with cognitive status and frontal lobe dysfunction independent of age, educational level, disease duration, CTG repeats, motor functional disability, fatigue, depression, and anxiety [172]. Anxiety or depression are common symptoms of various progressive diseases and may also contribute to functional impairment. It is still unclear whether depression in patients occurs as a direct result of brain dysfunction or secondarily due to disability or social isolation.

Excessive daytime sleepiness (hypersomnia) and sleep disorders, in general, are frequently reported symptoms in MD. The most frequent sleep disorders in MD1 are hypersomnia, sleep-disordered breathing, central and obstructive sleep apneas, periodic limb movements, and a narcoleptic-like phenotype, whereas restless legs syndrome, sleep-disordered breathing, and REM sleep without atonia seem to be the most frequent sleep disorders in MD2 [176–178]. Excessive daytime sleepiness may be attributed mostly to hypoventilation, but also it could be due to central dysregulation of sleep-wake modulation, poor sleep hygiene, or medication side effects [176]. Excessive daytime sleepiness also tends to persist despite successful treatment of sleep-disordered breathing in patients [179], thus supporting the hypothesis that hypersomnia is primarily caused by a central dysfunction of sleep regulation [179]. Although it was reported that subjective and objective daytime sleepiness in MD1 may be associated with the degree of muscular impairment [179], other authors showed that no clinical parameters appear to predict sleep apnea in MD1, but in MD2 the severity of sleep apnea was correlated with the degree of respiratory muscle involvement [180]. Pain as well may contribute to sleep fragmentation and excessive daytime sleepiness in MD2 [181]. Excessive daytime sleepiness is presented in about 70-80% of MD1 patients [179], while in MD2 hypersomnia is not so conclusive and the frequency of sleep complaints generally are about 60-70% [181].

Until now, little is known about changes in CNS causing cognitive deficits. On a molecular basis, toxic RNA inclusions may be involved in CNS alterations, but still little is known about molecular defects causing highly variable CNS symptoms mainly in MD1 [182,183]. Using brain positron emission tomography it was shown that the cognitive impairment and specific behavioral profile in both types of MD could be associated with hypoperfusion in the frontal and parieto-occipital regions of the brain [162,184]. MD2 patients had a bilateral decrease in regional cerebral blood flow of the orbitofrontal and medial frontal cortex, whereas MD1 patients had more widespread hypoperfusion that extended to the dorsolateral frontal cortex and subcortical regions [184]. It was also found that the impaired visual-spatial function in MD2 better correlates with a reduction in regional cerebral blood flow rather than with specific structural abnormalities observed on brain MRI [184]. On the other hand, there is also evidence that brain lesions in MD1 and MD2 consist of neurofibrillary tangles, which are neuropathological lesions globally referred to as tauopathies, thus a neurodegenerative disease that is characterized by intraneuronal protein aggregates of the microtubule-associated protein Tau in patient brains [182,185]. Moreover, several neurodegenerative diseases involve the dysregulation of splicing regulating factors and have been characterized as spliceopathies [182]. Although neurofibrillary tangles are observed in the MD brain, the question of whether MD is tauopathies remains a matter of debate. More likely it could be a result of the interplay between spliceopathy and tauopathy [182]. Nevertheless, this provides evidence that MD is not solely a muscular disease but that brain affection shares many similarities with tauopathies and other neurodegenerative diseases [185]. In summary, we can say that CNS dysfunction is most likely multifactorial.

6.2.4. Endocrine symptoms

Endocrine dysfunctions in myotonic dystrophy are frequent and the occurrence of endocrine abnormalities increases over time with the progression of the disease [186]. Endocrine abnormalities include insulin resistance with usually mild type-2 diabetes, thyroid dysfunction, hypogonadism, secondary hyperparathyroidism, or hyperlipidemia [186–189].

One of the major features of endocrine symptoms is the involvement of glucose metabolism with reduced insulin sensitivity and the development of type 2 diabetes mellitus or glucose intolerance [190]. The extent of insulin insensitivity varies in different studies for both types. In a cohort of 115 MD1 patients investigated for thyroid abnormalities, 13% of them had abnormal glucose tolerance results, and 25% had diabetes [191]. A much lower frequency of diabetes mellitus type 2, only 5%, revealed another extent study of endocrine function in

MD1 patients [192]. Other authors observed elevated basal insulin levels in 64 - 75% of MD2 patients or diabetes mellitus type 2 in 32% of these patients [53,193]. The frequency of diabetes mellitus in MD2 patients thus seems to be higher than reported in MD1. Nevertheless, it is probably caused by the later onset of MD2. The mechanism of the pathophysiology of diabetes mellitus in MD is explained as the pathogenic effect of expanded messenger RNA (mRNA) when altered insulin-receptor splicing leads to insulin insensitivity and diabetes mellitus [29,30,194]. Moreover, the recent data indicate that post-receptor signaling abnormalities in skeletal muscle could also contribute to MD insulin resistance regardless of alteration of insulin receptor splicing [195]. Not treated diabetes mellitus may complicate the disease above that by diabetic polyneuropathy with worsening of gait stability. Also could be the question of whether the increased frequency of diabetes mellitus type 2 is not influenced by other factors, such as metabolic syndrome with components like hypertension, central obesity, or hyperlipidemia. It was investigated that metabolic syndrome occurs in MD patients from 17% to 53% with a higher frequency in patients with MD2 compared to MD1, most likely due to the later onset and diagnosis of MD2 [193,196]. Metabolic syndrome is an important risk factor for the development of cardio- and cerebrovascular events, and further contributes to the consequences of multiorgan involvement in MD.

Thyroid abnormalities occur in MD with increased frequency and patients may acquire hypothyroidism or hyperthyroidism which may contribute to muscle weakness and fatigue. The functional failure of thyroid-stimulating hormone (TSH) secretion is common in MD [197,198]. In a big cohort of MD1 patients, the frequency of ultrasound goiter was about 40%, ultrasound nodules 60%, thyroidectomies 14%, and macro-papillary thyroid carcinoma 8% [191]. These and other authors also revealed in MD1 patients the thyroid dysfunction by abnormal thyroid function tests (7.8% of the patients had a TSH level below the lower limit and 13% above the upper limit of reference range; 50% of the patients had positive anti-thyroid peroxidase antibody levels) [191,192]. Similar findings in MD2 showed high TSH values in 9% of patients [189].

Hypogonadism (low serum testosterone levels) is one of the better-described endocrine dysfunctions in myotonic dystrophy. Testicular and tubular atrophy, oligospermia or azoospermia, and increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are common features described primarily in MD1 males with a frequency of 65–80% [199,200]. However, later primary hypogonadism was described to be common for both types of MD with a frequency of about 30 - 45% [53,192,201,202], even more, prevalent in the case

of the subclinical condition, that is elevated LH in presence of testosterone levels in the normal range [202]. Also, other authors confirmed that 38 - 51% of the MD1 patients have increased LH levels with low or normal testosterone levels, indicating absolute or relative androgen insufficiency [192,201]. Following the above, the FSH levels are also elevated in MD patients with reported frequency from 42% to 100% in type 2 and about 70% in type 1 [53,189,202]. Also, Sertoli cell hormones AMH and inhibin B seem to be reduced in most male patients with MD with suggesting that Sertoli cell hormones might be reliable markers for the evaluation of male reproductive capacity in patients with MD [202]. Total testosterone levels could negatively correlate with CTG repeats number in patients with MD1 [202]. Although MD1 and MD2 differ for the genes disrupted in their pathogenesis, hormonal features of hypogonadism show similar findings for both types indicating a similar pathological mechanism. It was described that CTG expansion in MD1 causes transcriptional silencing of the flanking Six5 allele, which has been demonstrated to results in a progressive decrease in testicular mass and that contributes to the male reproductive defects, because of a strict requirement of Six5 for both spermatogenic cell survival and spermiogenesis [203]. In healthy men generally, findings show that body composition could affect sex steroid hormone levels [204]. Similarly in MD was found that free testosterone levels were predicted by fat mass parameters, suggesting that increased adiposity might contribute with the genetic background to impair gonadal hormonal function also in patients with MD [202]. This proves the endocrinology study in MD1 patients that showed an increase in muscle mass and decrease in fat mass after testosterone administration thus demonstrate an improvement of body composition in patients with MD1 during the treatment of hypogonadism [205]. The increased fat mass in patients with MD could be considered a reflection of muscle-to-fat transdifferentiation [120]. Indeed, besides an increase of muscle fat mass, Italian researchers observed a significant increase in visceral fat mass as documented by increased abdominal adiposity, increased epicardial fat thickness, and increased prevalence of steatohepatitis in both patients with MD1 and MD2 [202]. These findings might suggest the effect of impaired muscle cells on the regulation of adipogenesis [202,206]. The increased adiposity might also determine the increase of serum estradiol and sex hormone-binding globulin (SHBG) levels [202]. Moreover, serum testosterone as well as AMH and inhibin B levels have been found reduced in men with metabolic syndrome [207,208].

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is seen in MD1. The abnormal diurnal rhythms of adrenocorticotropic hormone (ACTH) and cortisol have been shown in several reports of MD1 patients [205,209,210]. There was demonstrated

exaggerated ACTH secretion after exogenous corticotropin-releasing hormone (CRH) stimulation, indicating dysregulation of ACTH secretion, and hyporesponsiveness of the adrenal cortex to ACTH stimuli [205,209,211]. It was speculated on the abnormality of dihydropyridine-insensitive Ca2+ transport in the corticotrophs of MD1 patients with the suggestion that abnormality of cellular Ca2+ transport may underlie the disturbances of hypothalamic-pituitary-adrenal axis function in this condition [209]. MD1 patients also have disturbed diurnal rhythms of proinflammatory cytokines, especially increased production of interleukin-6 and tumor necrosis factor-alpha that may influence HPA axis function at several sites [211,212]. These cytokines are produced in adipose tissue and involved in many metabolic functions [213]. That adiposity may contribute to these disturbances, which may be of importance for decreased adrenal androgen hormone production and metabolic, muscular, and neuropsychiatric dysfunction in MD1 [211]. Studies about the adrenocortical activity in MD2 are lacking.

Hypercholesterolemia and hypertriglyceridemia are well-known conditions in both types of myotonic dystrophy and occurs up to around 60%, although it appears that hyperlipidemia is slightly more common in MD2 than in MD1 [189,193,201]. In the research of 115 MD1 patients, it was documented that about 25% of patients received statins, which proves the high frequency of hyperlipidemia in this disease [191]. Although is widely known that statins can cause muscle problems in MD (and other muscle diseases), lipid-lowering drugs have to be prescribed because of the increased risk of cerebrovascular diseases in patients with hyperlipidemia.

Secondary hyperparathyroidism with severe vitamin D deficiency is common in MD patients, rarely the primary hyperparathyroidism may occur too [187,188,192]. Therefore almost in all patients, hyperparathyroidism (increased parathyroid hormone) is associated with normocalcemia, rarely with hypercalcemia [187,192]. The most frequent hypovitaminosis D was found in a cohort of 115 MD1 patients investigated for thyroid abnormalities when a low vitamin D level was observed in about three-quarters of patients [191]. The direct correlation of vitamin D deficiency with the severity of genotype was also described [188]. Some of the MD1 patients have also hypophosphatemia associated with elevated parathyroid hormone levels [187]. The frequency of hyperparathyroidism is about 18% of patients without differences between MD types [187,192]. The exact mechanisms underlying vitamin D deficiency in MD is not clear. It has been suggested that the dysfunction of calcium metabolism in patients with MD1 could be because of renal parathyroid hormone (PTH) receptor dysfunction or disturbed intestinal calcium absorption [214,215]. Although some

studies sustain the hypothesis that cutaneous alterations, rather than malabsorption or liver dysfunction, might be responsible for vitamin D deficiency [188]. Vitamin D participates in bone and muscle metabolism, thus in association with other endocrine alterations described herein, might contribute in different ways to the metabolic syndrome predisposition. In addition, it was found that hypovitaminosis D correlates with increased adiposity [187]. Moreover, hyperparathyroidism may contribute to fatigue and muscle impairment [187]. An early diagnosis of primary or secondary hyperparathyroidism could be useful to prevent calcium metabolism disorders and their consequences on bone and muscle tissues.

Some studies showed that several endocrine abnormalities positively correlate with CTG triplet repeats in MD1. Numbers of CTG repeats correlated directly with plasma PTH, phosphate, LH, and tended to correlate with plasma testosterone in males [187,192].

It is also supposed that both populations of MD have a decrease in select hematologic counts, such as red blood cells, platelets, or hemoglobin [189,201]. But there are not enough studies to confirm these findings.

6.2.5. Reproductive symptoms

Reproductive abnormalities are a well-recognized finding in myotonic dystrophy. In men with myotonic dystrophy type 1, reproductive problems due to a high prevalence of testicular atrophy and oligospermia or azoospermia are well-known manifestations of the disease [199]. Local smooth muscle degeneration, i.e. a dysfunction of the testicular peritubular myoid cells and the corpus cavernosum smooth muscle, together with hypogonadism has been suggested to contribute to the male's erectile dysfunction in MD1 [216]. Histological abnormalities include hyalinization, atrophy, fibrosis of seminiferous tubules, and reduced sperm numbers [203]. Erectile dysfunction is reported to be one of the consequences of androgen deficiency in hypogonadism due to testicular diseases [217], as well as in late-onset hypogonadism due to aging [218]. In MD1 it was reported that the occurrence of erectile dysfunction was found approximately in 2/3 of the MD1 patients and was independent of the age of patients, but was correlated with other factors intrinsic to MD1, such as disease duration and severity and CTG expansion [217,219]. In MD1 women, fertility also appears to be impaired. The reduced ovarian reserve was demonstrated by lower levels of anti-Müllerian hormone (AMH) in MD1 women with clinically clear fertility impairment undergoing in vitro fertilization (IVF) [220], but also in the general MD1 female population [221]. Female patients with MD1 have also decreased ovarian sensitivity, with reduced response to ovarian stimulation and less favorable outcomes for IVF, suggesting poor ovarian condition [220,222,223]. Other findings show a

higher number of poor-quality embryos and lower pregnancy rates in MD1 women [224]. All the above confirms that decreased ovarian reserve is a general feature of MD1 female patients. In MD2 women, fertility appears to be preserved with normal AMH levels [221]. In MD2 men specific studies for fertility are lacking.

Compared to the general population, there is a higher rate of ectopic pregnancies, spontaneous abortion, stillbirth, placenta previa, and preterm labor in MD1 [225,226]. Preterm labor or late miscarriages could be also present in MD2 [226,227]. Preterm deliveries are recorded in about 31% of MD1 women, and less frequent (12.6%) in MD2 [226]. Polyhydramnios by a fetus with congenital MD1 may be the cause of pre-term labor [226]. Placenta previa, uterine muscle dysfunction, and muscle weakness can lead to prolonged labor or obstetric hemorrhage [225,226]. The delivery in patients with MD1 is more frequently by cesarean births (36.7%) and there are significantly more frequently abnormal fetal presentations (34.6%) [226].

Considering the possible influence of pregnancy on the disease course, the deterioration of symptoms of disease in pregnancy may occur in both types. This is mainly due to the effect of increased body weight on the patient's musculoskeletal system.

6.2.6. Gastrointestinal Symptoms

The involvement of the gastrointestinal tract in MD is frequent and may occur at any level from the pharynx to the anal sphincter, resulting from muscle involvement or myotonia involving the smooth or striated muscles of the gastrointestinal tract [228,229]. In the upper digestive tract, dysphagia, heartburn, regurgitation, and dyspepsia are the most common complaints, while in the lower tract, abdominal pain, bloating and changes in bowel habits are often reported [228,229]. Constipation or diarrhea, pseudo-constipation, or bloating are frequently reported symptoms in MD and these motility disorders are most likely caused by the involvement of smooth and striated muscles with reduction of gastrointestinal peristaltic movements [229,230]. Digestive symptoms may be the first sign of disease and may even precede significant muscle weakness [230]. For some patients, digestive symptoms are considered to be the most disabling consequence of the disease [228]. It seems a low correlation between the degree of skeletal muscle involvement and the presence and severity of gastrointestinal involvement. The drugs recommended for treating gastrointestinal complaints such as prokinetic, anti-dyspeptic drugs, and laxatives, are mainly aimed at correcting motility disorders [229].

Swallowing problems are typical for MD1 patients because of myotonia and weakness of oropharyngeal muscles or reduced esophageal motility [231]. Dysphagia is such a big risk for aspiration and cause of aspiration pneumonia. Also among MD2 patients, dysphagia is present, but it is generally mild and does not lead to weight loss or aspiration pneumonia [232].

There is a relatively frequent appearance of abnormally elevated liver enzyme levels gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and lactate dehydrogenase (LD) in both types of MD [189,201,233,234]. The elevated levels of AST, ALT, and LD enzymes is caused, at least in part, by underlying muscle damage in MD and are associated with elevations of creatine kinase [201,233], whereas the elevation of GGT is suggested to be caused by cell membrane defect affecting the contractility of bile ductules and bile canaliculi [233,235]. Another interpretation is that the elevation of GGT levels represents dysfunction of the hepatocyte [201]. Delayed emptying of the gallbladder may increase the risk for gallstones [12].

A rare gastrointestinal manifestation of MD could be disturbances of the pancreatobiliary system, resulting from the dysfunction of Oddi sphincter and gallbladder myotonia, which could lead to idiopathic pancreatitis [236,237]. Sphincter Oddi dysfunction results from spasms of both the distal common biliary duct and the duct of Wirsung [236].

6.2.7. Autoimmune diseases

It has been hypothesized about the association between autoimmune laboratory dysfunction and MD2, but not MD1 [238]. The observations showed that the frequency of autoimmune diseases (21% vs 2%) and the frequency of autoantibodies (25% vs 2%) were both significantly higher in MD2 patients compared with MD1 patients [238]. Also, other authors reported in MD2 patients the low serum levels of immunoglobulin (Ig) G in 65 - 75% and IgM levels in 11 - 12%, but normal IgA levels [53,189]. The elevation of IgE values in 36% and low absolute lymphocyte counts in 54% of this cohort of patients were also found [189]. This could suggest an impaired immune response mechanism in MD2. However, marked decrement IgG levels only, but not so significant IgE, IgM levels, and not at all IgA level, could indicate selectively impairment of IgG via an RNA mediated process [189]. Some authors also associate a higher prevalence of autoimmune chronic gastritis and MD2 [239] with evidence of the significantly higher frequency of gastrointestinal symptoms and vitamin B12 deficiency among MD2 patients [228,238].

The cause of autoimmune dysfunction is still being under research. The recent findings identify CNBP as an important regulator of interleukin-12 gene transcription and Th1 (T helper type 1) immunity [240]. Other similar observations identify CNBP acts as a key transcriptional regulator of sustained expression of interleukin-6, required for activating and maintaining the immune response [241]. Also, it has been demonstrated that the RNA alternative splicing factor MBNL1 is essential for normal thymus development and function, and deregulation of MBNL1 in myotonic dystrophy leads to thymic hyperplasia with thymocyte accumulation [242].

6.2.8. Kidney dysfunction

Patients with MD1 could be at risk of renal dysfunction. Because muscle atrophy decreases the serum creatinine level, the renal function could be assessed using cystatin C, which also represents an indicator of kidney function, but one that is not affected by changes variables such as muscle volume, food intake, or exercise [243]. A recent paper found the high circulating cystatin C levels in MD1 patients, potentially predictive of subsequent kidney damage and failure [244]. Moreover, in two autopsies of forty years old cases, nephrosclerotic changes were observed that suggested a disease-specific pathomechanism for renal dysfunction in MD1 [244]. Therefore, renal function should be carefully monitored in patients with MD1. Also, another study that measured glomerular filtration rate showed a slight decrease in renal function of most MD1 patients [245]. The association between renal function and the number of CTG repeats, a marker of disease severity, shows contradictory results [244,245]. Polycystic disease of the kidneys was described in some families with MD1 in the past before genetic testing [246]. Also, a very recent case reported the possibility of association MD1 with autosomal dominant polycystic kidney disease as a “double trouble” condition [247]. Nevertheless, this may be only a co-occurrence of two conditions. On the other hand, there is currently a growing consensus about the association of certain neoplasms and MD1 and consideration of polycystic kidney disease as a “tumor-like” disease because of some pathophysiological characteristics shared with cancer [248].

6.2.9. Orthopedic disorders

Orthopedic problems may complicate already existing patients’ immobility due to muscle weakness. The most common orthopedic impairments are contractures, foot deformities, and spinal deformities in MD1 patients [249,250]. Contractures are typically located distally in the lower extremities, but can also occur in the hip or shoulder joints [249]. Spinal deformities

include scoliosis, hyperkyphosis, and a rigid spine with pathological chin-sternum distance [249].

6.2.10. Hearing Impairment

Hearing impairment has been described in MD2 patients and showed that a mild to moderate hearing impairment was present to some degree in 62% of examined patients (mild in 39%, moderate in 21%, and severe in 2% of patients with MD2) [251]. The study suggests that sensorineural hearing impairment is located in the cochlea, significantly correlates with age, and may lead to early presbycusis [251]. This finding correlates with the considered interpretation of MD as premature aging diseases described above [25]. Similar results of cochlear impairment have been described also in MD1 patients, even in patients without evidence of hearing loss [252].

6.2.11. Cancer

There is evidence that patients with myotonic dystrophy are at excess risk of cancer, although inconsistencies regarding affected anatomic sites persist [253–257]. Results of the survey from the UK MD1/MD2 registry showed 12.4% of at least one benign tumor and 6.2% at least one malignant tumor with the highest incidence of skin tumor, then breast and female reproductive system tumors, and confirm potential genetic contribution in tumor predisposition in myotonic dystrophy [255]. Almost all of the tumors in the mentioned survey occurred in MD1 patients [255]. Increased risk of tumors only in the MD1 subtype was also found in another study, where the history of the benign or malignant tumor was 10.4% [256]. Similar, even more frequent, findings of the prevalence of benign (21.2%) and malignant tumors (6.7%) have been published by Italian authors when the most common occurrence was the cancers of the skin (31.6%), thyroid (21.0%), ovary (10.5%), breast (10.5%), and uterine fibroid in women (37.6%) or pilomatricoma in men (28.6%) [257]. It was also found no association between tumor development and common cancer risk factors in MD1 patients, supporting a pathogenic link between tumors and MD itself [257]. Another study determined the increased oncologic risk in MD1 for gynecologic (ovary and endometrium), brain, and thyroid cancer and revealed significant downregulation of the microRNA-200c/141 tumor suppressor family [258]. Similarly, other studies showed an increased risk of thyroid cancer and choroidal melanoma and, possibly, testicular and prostate cancers [254] or cancers of the endometrium, brain, ovary, and colon [253] or testicular cancer, endometrial cancer, and non-Hodgkin lymphoma [259]. It was also recommended careful evaluation of MD patients with

new central nervous system symptoms because of the high relative risk of MD-related brain tumors [260]. In accordance with the findings above the meta-analysis of 5 studies of cancer risks in MD showed the most significant risk for cancer of the endometrium and cutaneous melanoma in all studies [261].

6.2.12. Peripheral neuropathy

Peripheral neuropathy is mostly caused by metabolic and endocrine dysfunctions. In the cause of myotonic dystrophy, there is a theory whether peripheral neuropathy is a direct multisystem manifestation of the disease [118,262], not the result of other organ involvements, like diabetes mellitus.

The incidence of peripheral nerve involvement seems to be similar in both types of myotonic dystrophy, and criteria of polyneuropathy were described to be fulfilled in about 13% of patients with both types [119]. Some authors admit the presence of peripheral polyneuropathy in MD1, but this especially in later stages of the disease and with certain metabolic dysfunctions [263,264]. In MD2 the polyneuropathy is described to be subclinical, and no correlation was found between its presence and patient age or disease duration [119]. Therefore it mostly suggests, that affection of the peripheral nervous system is secondary to metabolic and endocrine dysfunctions [119]. Nevertheless, some authors admit the presence of peripheral neuropathy as one of the multisystemic manifestations of the disease [118].

6.2.13. Skin changes

Skin abnormalities were described to be frequently observed in both types of MD with a significantly higher frequency of dysplastic nevi, alopecia, xerosis, and seborrheic dermatitis, and correlate with genotype severity and serum vitamin D levels [265]. Skin abnormalities are also regarded as indicators for premature aging [265]. Skin examination is therefore highly informative in these patients.

The knowledge of all these extramuscular symptoms is important for their early identification. Most of these comorbid conditions are potentially treatable and early treatment improves clinical outcomes for this patient population.

It is important to exclude another possible cause of organ dysfunction before assigning some patient symptoms to the multisystem manifestation of the disease. It is important also to keep in mind the possibility of a “double trouble” condition in patients affected by rare genetic diseases, especially when atypical clinical manifestations are observed [247]. The “additive"

mutations in MD patients can cause a more severe phenotype than expected, so we can mistakenly suppose these atypical clinical manifestations as a “more extended clinical spectrum” of multisystem disease. The coincidence of MD with other hereditary diseases with some additional mutations was recorded in the literature. It has been described MD1 associated with facioscapulohumeral muscular dystrophy [266], Charcot-Marie-Tooth neuropathy [267], or polycystic kidney disease [247], and already described here co-segregation of MD2 with ion channel genes CLCN1 or SCN4A mutations [98–101].

7. Quality of life

The lives of patients with MD are affected by a variety of symptoms that have different levels of significance in different patients.

Among MD1 patients the excessive daytime sleepiness, poor sleep quality, and fatigue are prominent complaints and have a significant impact on their quality of life [268,269]. Concurrently patients identified fatigue and limitations in mobility as the symptomatic themes that have the greatest effect on their lives [269]. Sleep-disordered breathing is a frequent manifestation in both forms of myotonic dystrophies, however more often in patients with MD1 [180]. Thus nocturnal hypoventilation represents the serious complication of disease with a significant impact on the quality of life, morbidity, and mortality [81,270].

Significant predictors of worse quality of life in MD2 patients are usually older age, worse muscle strength, and a higher level of fatigue [271]. The MD2 patients complain of the inability to do activities and fatigue as the most frequent symptom that impacts their lives [97,268]. Unemployment is therefore a common problem in these patients. The pathophysiology of fatigue is probably multifactorial with contributions of central nervous system dysfunction, muscle weakness, depression, thyroid dysfunction, or medications [268]. Also in MD2 sleep quality is poor, and is not explained by depression or other comorbidity but mainly due to sleep disturbances as a result of nocturnal pain [268].

Patients with MD1 have a reduced life expectancy and a mortality rate is approximately 7.3 times higher than the age-matched general population [7]. Life expectancy is reduced due to increased comorbidities such as pneumonia, respiratory failure, cardiac arrhythmia, and neoplasia. The most frequent causes of death in MD1 are cardiorespiratory disorders that are responsible for 70% of the mortality in MD1 [7,143]. In particular, respiratory failure is the leading cause of death in MD1 patients [7]. Cardiac arrhythmias, especially heart block, are that the second most common cause of death in these patients [82]. The life expectancy of patients with MD2 is not expected to be reduced.

8. Diagnostics

8.1. Laboratory tests

Creatine kinase (CK) is an enzyme that exists in skeletal and heart muscle, and in other tissues, so CK blood levels can rise due to many causes. CK levels are often significantly elevated in neuromuscular conditions, including MD, because of leaks of the enzyme from the skeletal muscle tissue associated with degeneration. In some cases elevated CK levels can help to confirm a suspected muscular problem before disease symptoms are evident. It is important to note that patients with MD can have a wide range of elevated CK levels. In the early stages of MD, CK levels are much higher than in later stages, because muscle degeneration is more rapid in earlier stages. Later when more muscle tissue is replaced by fibrotic tissue the less degeneration occurs, thus lower CK levels are more common in the late stage of the disease. Therefore, the CK levels do not provide accurate information about the current disease status. In MD CK level is usually slightly increased, the maximum about 10 times, in some patients can be even normal [6].

As for other hereditary genetic diseases, the verification of known mutation by genetic tests is the key diagnostic method in MD. The mutation can be confirmed by polymerase chain reaction (PCR) and Southern Blot analysis [272]. PCR analysis is used to detect repeat lengths less than 150 and Southern blot analysis or triplet-repeat primed PCR, or small-pool PCR to detect larger expansions with long repeats [272]. Predictive testing of relatives may help to find asymptomatic persons and thus help in family planning with the performance of prenatal and preimplantation diagnosis. The family history of the autosomal dominant transmission of disease (symptoms) is often distinctive enough to make a clinical diagnosis.

It seems that patients with MD1 could have a higher level of tumor necrosis factor-alpha (TNF-α) [273]. It was described that it might be rather a simple marker of disease activity and might represent an adjunctive criterion for disease staging than play a role in the pathogenesis of MD [273]. Higher levels of TNF-α have also been found in Becker and Duchenne muscular dystrophy and may prove to be a useful marker of disease activity [127].

Sometimes the wide clinical spectrum of MD2 phenotype especially makes the clinical diagnosis more difficult.

8.2. Muscle biopsy

Muscle biopsy is not necessary for the diagnosis, but the histological features of muscle in MD are characteristic. The findings of muscle biopsy are very similar in both types of MD and show a high number of internal nuclei, increased fiber size variation, basophilic

regenerating fibers, splitting fibers, fibrosis, and adipose deposition [18,274,275]. All findings occur in varying degrees depending on the extent of muscle involvement [18]. In MD2 we can observe a predominant type 2 fiber atrophy in contrast to the type 1 atrophy in MD1, also central nucleation selectively affects type 2 fibers and the atrophic nuclear clumps express fast myosin isoform (type 2 fiber) [32,274–276]. All these findings above indicate that MD2 is predominantly a disease of type 2 myofibers [274,275]. Interestingly, severely atrophic fibers with pyknotic nuclear clumps observed also in neurogenic atrophy are frequently found in MD2 biopsy even before the occurrence of muscle weakness [32]. On the contrary in MD1, highly atrophic fibers and nuclear clumps are not present at earlier stages of MD1 muscle biopsy [32].

In MD-related cardiac disease have been reported nonspecific histopathological findings of the heart as interstitial fibrosis, degeneration, fatty infiltration, myocyte hypertrophy, variation in myocyte size, focal myocarditis with lymphocyte infiltration, muscle fiber re-arrangement, or focal vacuolar myocyte degeneration [127,277,278].

Inclusions formed by expanded RNA and MBNL proteins can also be observed in the tissues of MD1 and MD2 patients using in situ hybridization and immunofluorescence [279].

8.3. Electromyography

The combination of myotonic discharges and myopathic reorganization of motor unit potentials on electromyography are characteristic for this disease. Myotonic discharges are pathognomic for MD and other muscle channelopathies and they represent a very valuable diagnostic method [95,96]. The myopathic pattern on electromyography may not be present in younger patients with MD1 or patients with MD2 at an earlier stage of the disease [6,95]. In patients with MD we can also find the combination of myotonic and complex repetitive discharges which reflect dystrophic changes of muscle fibers.

8.4. MRI

Myotonic dystrophy such as other dystrophies have often a characteristic pattern of muscle affliction on MRI. Those findings differ between both types but also show some overlap. In both types, we can find fatty infiltration of muscle tissue [280]. It also seems that some muscles in both types may be affected before weakness is clinically noted and vice versa [280].

MD1 is typically characterized by distal more than proximal muscle involvement showing predominant affliction of the soleus, medial gastrocnemius, and proximally the anterior thigh

compartment with relative sparing of the rectus femoris (Figure 3) [80,280,281]. The anterior compartment (tibialis anterior muscle) was observed with later involvement and the posterior tibialis muscle is spared [280]. MD1 patients show signs of fatty degeneration or oedematous changes in the affected muscles on muscular MRI [281].

In contrast to MD1, patients with MD2 are less affected based on MRI findings [280]. Affected patients show more involvement of the proximal muscles especially with the affliction of the quadriceps (Figure 3) [280,281]. A whole-body MRI study including MD1 and MD2 patients showed that most of the affected MD2 patients showed damage predominantly of the trunk muscles (such as the erector spinae and gluteus) and in some cases involvement of the proximal and lower leg muscles with sparing of the rectus femoris and gracilis muscles in all MD2 patients [80].

9. Management

There are currently no curative or disease-modifying therapies, although clinical treatment trials have become more promising. There are potential strategies including genome editing, small molecule therapeutics, and antisense oligonucleotide-based therapies to target the pathogenesis of type 1 and type 2 myotonic dystrophies at the DNA, RNA, or downstream target level [282]. Antisense and other RNA-mediated technologies have been applied to target toxic-repeat mRNA transcripts to restore MBNL protein function in MD1 models, such as cells and mice, and humans. This technique has promising results in MD1 therapeutics by alleviating pathogenic phenotypes [183,282].

To reduce the impact of muscular impairment and other systemic involvement we use periodic clinical surveillance. Currently, there is an increasing international consensus on the necessity of the existence of a multidisciplinary team to provide comprehensive and coordinated clinical care. A multidisciplinary approach consists of a team of neurologists, genetic counselors, pulmonologists, cardiologists, ophthalmologists, pediatricians, internists, and psychologists/psychiatrists [82]. Management focuses on genetic counseling, preserving function and independence, preventing cardiopulmonary and ophthalmologic complications. Genetic counseling is strongly recommended and should include education regarding inheritance, anticipation, or maternal bias. Intense prenatal care and counseling should be provided to female patients desiring to have children. Prenatal testing is available and can be performed before implantation or in utero [283].

Monitoring of cardiorespiratory function with an electrocardiogram, echocardiogram, and spirometry is necessary on regular periods. An annual 12-lead electrocardiogram (ECG) and

echocardiogram (or cardiac MRI) every 2–5 years is recommended [82]. Symptomatic patients with a normal ECG should undergo a cardiologic investigation with extended cardiac monitoring [82]. A pacemaker or implantable defibrillator is recommended for patients with clinically significant cardiac abnormalities [284]. Spirometry should include the examination of seated and supine force vital capacity (FVC), and forced expiratory volume in 1 s (FEV1). If hypoventilation or pulmonary restriction is reported, a careful pulmonary examination should be performed. Also, polysomnography should be performed on all patients suspected of hypoventilation or apnea. Non-invasive positive-pressure ventilation should be tried for respiratory insufficiency, hypoventilation, or sleep apnea, and bilevel positive airway pressure is recommended for patients with respiratory muscle weakness [82]. Regular ophthalmologic examination is necessary for the early detection of cataracts [82]. Monitoring of endocrine function by blood sampling is also required in MD. Periodic glucose tests (fasting glucose tolerance test, glycosylated hemoglobin), lipids, liver function, and thyroid function testing should be performed. Males with testicular failure (erectile dysfunction, infertility) should be referred to specialists. Females with dysmenorrhea, irregular menstruation, or infertility should be referred to gynecology and obstetrics.

An important part of care is the symptomatic treatment of pain, myotonia, or hypersomnolence. Muscular pain is a frequent and difficult problem in MD and for some patients is pain the most disabling symptom of the disease. Most of the patients usually use paracetamol, non-steroidal anti-inflammatory drugs, tramadol, or other opiates, but sometimes pain has a poor response to these common analgesics. Antineuralgic therapy should be initiated when there is no effect of common analgesics or pain appears to be neuropathic. In specific circumstances, antimyotonia therapy is helpful, especially if muscle stiffness is frequent and severe. Sodium channel blockers, such as mexiletine, phenytoin, procainamide, propafenone, flecainide, carbamazepine, and quinine, have been reported to improve myotonia [82]. Methylphenidate or modafinil could be tried for excessive daytime sleepiness [285,286]. Vitamin D supplementation is beneficial not only to patients with secondary hyperparathyroidism but also with primary hyperparathyroidism and coexisting vitamin D deficiency.

Symptomatic treatment of muscle weakness includes occupational therapy, physical therapy, speech therapy, swallow evaluation, or assistive devices if necessary. A need for supportive care, such as a cane, walker, or wheelchairs, is more often in MD1. Regular low to moderate intensity strength training or aerobic exercise programs might optimize muscle and cardiorespiratory function and prevent additional atrophy and deconditioning in people with a

muscle disease [287]. However, there is insufficient evidence to conclude that exercise offers benefits in preserving muscle strength [287]. In patients with significant weight loss or malnutrition, consultation with nutrition specialists should be considered, or even feeding tube placement. Surgery is indicated for severe foot deformities or contractures in MD1 patients [249].

As a rule, general anesthesia should be avoided and regional anesthesia should be used when possible [88]. Patients with advanced muscle weakness are at increased risk of perioperative acute respiratory failure. Therefore, pre-operative spirometry and cardiology assessment and careful perioperative cardiopulmonary monitoring are recommended. The need for post-surgically intensive care unit admission even noninvasive ventilator assistance is possible. MD patients are not more susceptible to the development of malignant hyperthermia. MD1 patients are more sensitive to the respiratory depressant effects of commonly used premedications, e.g. opioids and benzodiazepines [288]. If possible, it is recommended to avoid muscle relaxants altogether. When muscle relaxation is required, use non-depolarizing muscle relaxants and avoid a depolarizing muscle relaxant (succinylcholine), because of muscle rigidity and prolonged laryngospasm after succinylcholine administration [289]. The volatile anesthetic may exacerbate a patient's cardiomyopathy, secondary to their myocardial depressive effects [88]. In addition to medications, the cold temperature may trigger myotonia, therefore, hypothermia during surgical procedures should be avoided [88].

10. Literature

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11. Used shortcuts

ACTH - adrenocorticotropic hormone

ALP - alkaline phosphatase

ALT - alanine aminotransferase

AMH values - anti-Müllerian hormone

AST - aspartate aminotransferase

ClC-1, CLCN1 - muscle-specific chloride voltage-gated channel 1

CELF1 - CUGBP/Elav-like family member 1

CNBP - nucleic acid-binding protein gene

CNS - central nervous system

CRH - corticotropin-releasing hormone

CUGBP1 - CUG-binding protein 1

DNA - deoxyribonucleic acid

DMPK - dystrophia myotonica-protein kinase gene

ECG - electrocardiogram

EMG - electromyography

FEV1 - forced expiratory volume in 1 s

fMRI - functional magnetic resonance imaging

FSH - follicle-stimulating hormone

FVC - force vital capacity

GGT - gamma-glutamyl transferase

HPA - hypothalamic-pituitary-adrenal

Ig - immunoglobulin

mRNA - messenger RNA

IQ - intelligence quotient

LD - lactate dehydrogenase

LH - luteinizing hormone

MBNL1 - muscleblind–like protein 1

MD - Myotonic dystrophy

MD1 - Myotonic dystrophy type 1

MD2 - Myotonic dystrophy type 2

MRI - magnetic resonance imaging

PCR - polymerase chain reaction

PDM - Proximal myotonic dystrophy

PROMM - Proximal myotonic myopathy

PTH - parathyroid hormone

RNA - ribonucleic acid

TSH - thyroid-stimulating hormone

QST - Quantitative Sensory Testing

SCN4A - sodium channel type 4 subunit alpha

SK3 - calcium-activated potassium channel

ZNF9 - zinc finger 9 gene

12. List of tables

Table 1. Genotype-phenotype correlations in MD1. Correlations between phenotype and number of repetitions in MD1.

Phenotype	Number of CTG-repeats	Age of manifestation	Symptoms
pre-mutation phenotype	38 – 49	-	typically without clinical symptoms, risk of having children with larger expanded repeats
mild phenotype, late-onset form	50 – 100	20 – 70	mild myotonia, cataracts
classic phenotype, adult-onset form	50 – 1000	20 – 30	distal weakness, clinical myotonia, cataracts, other extramuscular symptoms
early-onset form: childhood and juvenile	50 – 1000 (typically > 800)	childhood:1 – 10 juvenile:10 – 20	learning difficulties, low intelligence quotient
congenital form	> 1000	from the birth	severe generalized and facial weakness, facial dysmorphia, respiratory insufficiency, cognitive impairment, mental retardation

Table 2. Comparison of clinical manifestations between MD1 and MD2.

	MD1	**MD2**
General features		
Age of onset	Depends on CTG-repeat-size, from birth to adulthood, usually 20-40 years	usually 30-50 years, but can be 10-60 years
Family history	anticipation phenomenon (increasing severity of symptoms throughout generations)	no evidence for anticipation, variability in symptoms
Congenital form	present	absent
Core features		
Myopathic face	yes	no
Forehead balding	yes	no
Muscle symptoms		
Muscle weakness	predominant distal	predominant proximal and axial

Facial and jaw weakness, ptosis	frequent	usually absent
Bulbar symptoms, dysphagia	frequent, nasal speech	usually absent, only dysphagia
Respiratory muscles weakness	frequent	exceptional
Sternocleidomastoid weakness	significant	present, but less significant
Muscle atrophy	early	usually absent
Calf hypertrophy	absent	present
Myotonia	severe (typically in adults)	mild or none, usually in <50%
Myalgia	yes, but usually less reported	usually
Systemic features		
Cataracts	present	present
Cognitive disorders	prominent	not apparent
Cardiac arrhythmias	present	less often
Daytime sleepiness	frequent	unusually
Life expectancy	reduced	normal range

13. List of figures

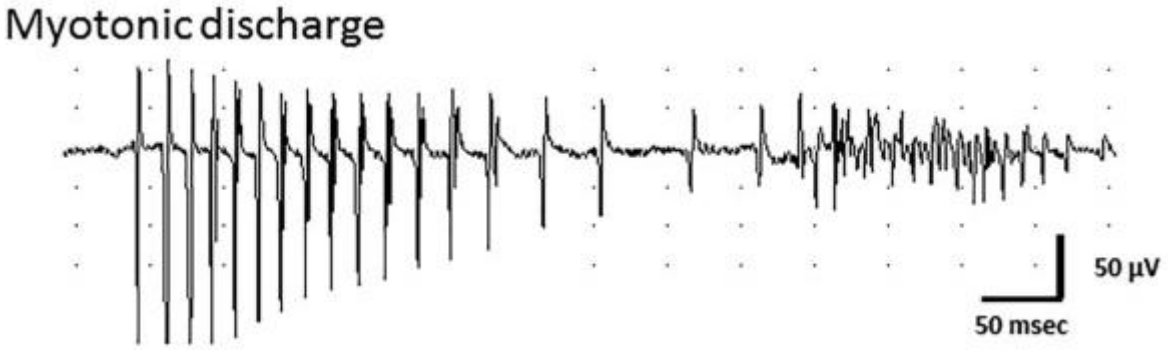

Figure 1. Myotonic discharge. The electrical activity of one muscle fibre. „Waxing and waning“ appearance caused by fluctuation of amplitude and frequency (maximum firing rates of 40–100 Hz) [290].

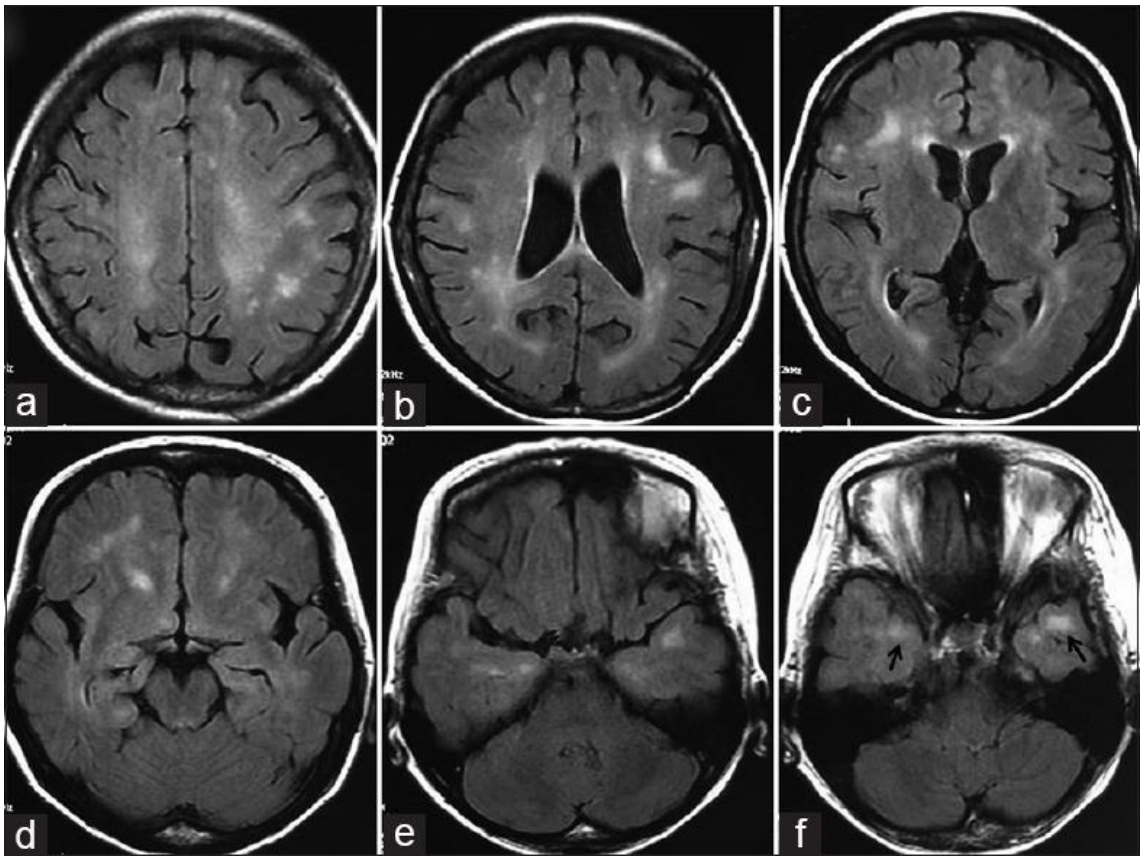

Figure 2. The axial brain magnetic resonance images in a patient with MD1. (a-d) White matter hyperintense lesions in both subcortical and periventricular areas, single or confluent; (e-f) Areas of high signal in the subcortical white matter of the anterior temporal lobes (arrows) [291].

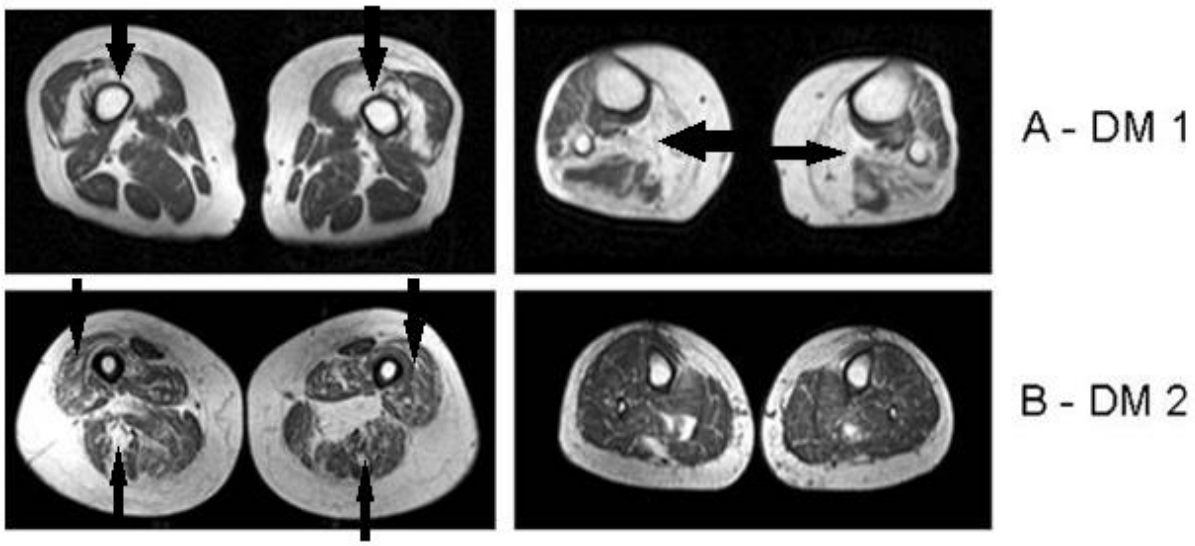

Figure 3. Muscle MRI of lower extremities [281]. (A) MD1 is typically characterized by distal more than proximal muscle involvement showing predominant affliction of the soleus, medial gastrocnemius, and proximally the anterior thigh compartment with relative sparing of the rectus femoris. (B) MD2 shows more involvement of the proximal muscles with the affliction of the quadriceps and sparing of the rectus femoris and gracilis muscles. Arrows show predominant affliction.

14. List of student's literature

I. List of publications

A. In impact Czech or foreign journals:

1. **Parmová O**, Voháňka S, Fajkusová L, Stehlíková K. Co-occurrence of the Gene ZNF9 Mutations (Myotonic Dystrophy Type 2) and Gene CLCN1 (Myotonia Congenita) in One Family – a Case Report. Cesk Slov Neurol N 2013; 76/109(5): 648-65. ISSN 1210-7859. IF 0,366.
2. Strenková J, Voháňka S, Haberlová J, Junkerová J, Mazanec R, Mrázová L, **Parmová O**, Ridzoň P, Staněk J, Šišková D, Vondráček P, Brabec P, Šnajdrová L. REaDY – Czech Registry of Muscular Dystrophies. Cesk Slov Neurol N 2014; 77/110(2): 230-234. IF 0,319.
3. Horáková M, Horák T, **Parmová O**, Voháňka S. Validation of questionnaire for patients with myotonia – Czech version of Myotonia Behaviour Scale. Cesk Slov Neurol N 2018; 81(5): 582-585. doi: 10.14735/amcsnn2018582. IF 0,355; Q4 clinical neurology.
4. Horáková M, Horák T, **Parmová O**, Bednařík J, Voháňka S. Quantitative myotonia assessment with a commercially available dynamometer in myotonic dystrophy types 1 and 2. Muscle Nerve. 2019, 59(4):431-435. doi: 10.1002/mus.26401. Epub 2019 Jan 9. PMID: 30575988. IF 2,393; Q3 clinical neurology.
5. **Parmová O**, Vlčková E, Bednařík J, Voháňka S. Neuropathic pain component in patients with myotonic dystrophy type 2: a pilot study. Cesk Slov Neurol N 2019; 115(3): 322-332. doi: 10.14735/amcsnn2019322. IF 0,39; Q4 clinical neurology.
6. **Parmova O**, Vlckova E, Hulova M, Mensova L, Crha I, Stradalova P, Kralickova E, Jurikova L, Podborska M, Mazanec R, Dusek L, Jarkovsky J, Bednarik J, Vohanka S, Srotova I. Anti-Müllerian hormone as an ovarian reserve marker in women with the most frequent muscular dystrophies. Medicine (Baltimore). 2020 Jun 5;99(23):e20523. doi: 10.1097/MD.0000000000020523. PMID: 32502004. IF 1,552; Q3 medicine general and internal in 2019; (IF 1,87; Q2 medicine general and internal in 2018).

B. In Czech or foreign journals without impact factor:

1. **Parmova O**, Vohanka S, Strenkova J. The Character and Frequency of Muscular Pain in Myotonic Dystrophy and Their Relationship to Myotonia. Int J Neurol Neurother 2014, 1:1. DOI: 10.23937/2378-3001/1/1/1009. ISSN: 2378-3001
2. **Parmová O**, Voháňka S. The onset of pain in myotonic dystrophy. Neurol. praxi 2016; 17(4): 240-243. DOI: 10.36290/neu.2016.050
3. Mensová L, **Parmová O**. Nationwide screening of Pompe disease in patients with unspecified muscle weakness, hyperCKemia, and respiratory insufficiency. Neurol. praxi 2018; 19(4): 306-308. ISSN: 1213-1814; 1803-5280.
4. **Parmová O**, Mensová L, Vohanka S, Mazanec R. Nationwide screening of Pompe disease in patients with unspecified muscle weakness, hyperCKemia, and respiratory insufficiency: preliminary results. Neurol. praxi 2020; 21(Suppl.B): 3-9. DOI:10.36290/neu.2020.064.

II. List of abstracts

A. In impact Czech or foreign journals:

1. Vohanka S, Parmova O, Strenkova J. Pain in patients with myotonic dystrophy: Comparison between type 1 and type 2. Neuromuscular Disorders 2013; 23 (9-10): 834-835.
2. Parmová O, Voháňka S, Strenková J. Urinary and fecal incontinence in patients with myotonic dystrophy. Cesk Slov Neurol N 2013; 76/109 (Suppl 2).
3. Voháňka S, Parmová O, Bednařík J, Fajkusová L. Myotonic spectrum in the Neuromuscular Center of the University Hospital Brno. Cesk Slov Neurol N 2014; 77/110 (Suppl).
4. Parmová O, Voháňka S. Spectrum and frequency of system disorders in patients with myotonic dystrophy. Cesk Slov Neurol N 2014; 77/110 (Suppl).
5. Parmova O, Vohanka S, Strenkova J. Frequency of multisystem abnormalities among Czech patients with myotonic dystrophy. Neuromuscular Disorders 2014; 24 (9-10): 891-892.
6. Vohanka S, Parmova O, Mazanec R, Vondracek P, Mrazova L, Haberlova J, Brazdilova M, Strenkova J, Brabec P. Czech national registries of hereditary neuromuscular disorders. Neuromuscular Disorders 2014; 24 (9-10): 892-892.
7. Vohanka S, Parmova O, Strenkova J. Lower Urinary Tract and Bowel Dysfunction in Patients with Myotonic Dystrophy. Poster Sessions Abstract Books. Journal of Neuromuscular Diseases 2014; 1 (s1): S81-S403. DOI: 10.3233/JND-149002
8. Parmová O, Voháňka S. Spectrum of less known clinical problems in patients with myotonic dystrophy. Cesk Slov Neurol N 2015; 78/111(1): 108-121.
9. Vohanka S, Parmova O, Mazanec R, Strenkova J, Ridzon P, Ehler E, Vavra A, Forgac M, Junkerova J, Bozovsky T, Kunc P. Myotonic dystrophy in Czech Republic: data from the national registry. J Neurol Sci 2015;357:e347–e348. DOI:https://doi.org/10.1016/j.jns.2015.08.1232.
10. Vohanka S, Parmova O, Mazanec R, Strenkova J, Ridzon P, Ehler E, Forgac M, Junkerova J, Bozovsky T, Kunc P. Czech National Registry of Myotonic Disorders. Cesk Slov Neurol N 2016; 79/112(4): 471-484.
11. Vohanka S, Bednarik J, Parmova O, Chmelikova M, Fajkusova L. Hereditary muscle disorders in Middle Europe: data from hospital registry. Poster Sessions Abstract Books. Journal of Neuromuscular Diseases 2016; 3 (s1): S1-S231.

12. Parmová O, Vlčková E, Bednařík J, Voháňka S. Does pain in myotonic dystrophy have a neuropathic component? Cesk Slov Neurol N 2017; 80/ 113 (Suppl 2).
13. Tvrdá M, Parmová O, Rajdová A, Vlčková E, Voháňka S. Impairment of thin nerve fibers in patients with myotonic dystrophy type 2. Cesk Slov Neurol N 2017; 80/ 113 (Suppl 2).
14. Vohanka S, Parmova O, Fajkusova L, Mazanec R, Strenkova J, Ridzon P, Ehler E, Forgac M, Junkerova J, Haberlova J, Stanek J. Czech national registry of facioscapulohumeral muscular dystrophy. Neuromuscular Disorders 2017; 27 (Suppl 2): S129-S130.
15. Horáková M, Horák T, Parmová O, Voháňka S. Quantitative myotonia assessment. Cesk Slov Neurol N 2018; 81(6): 716-726.
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15. List of commented works

15.1. **Parmova O**, Vlckova E, Hulova M, Mensova L, Crha I, Stradalova P, Kralickova E, Jurikova L, Podborska M, Mazanec R, Dusek L, Jarkovsky J, Bednarik J, Vohanka S, Srotova I. Anti-Müllerian hormone as an ovarian reserve marker in women with the most frequent muscular dystrophies. Medicine (Baltimore). 2020; 99(23):e20523. doi: 10.1097/MD.0000000000020523. PMID: 32502004

15.2. Horáková M, Horák T, **Parmová O**, Bednařík J, Voháňka S. Quantitative myotonia assessment with a commercially available dynamometer in myotonic dystrophy types 1 and 2. Muscle Nerve. 2019; 59(4):431-435. doi: 10.1002/mus.26401. Epub 2019 Jan 9. PMID: 30575988

15.3. **Parmová O**, Vlčková E, Bednařík J, Voháňka S. Neuropathic pain component in patients with myotonic dystrophy type 2: a pilot study. Cesk Slov Neurol N 2019; 115(3): 322-332. doi: 10.14735/amcsnn2019322

15.1. **Parmova O, Vlckova E, Hulova M, Mensova L, Crha I, Stradalova P, Kralickova E, Jurikova L, Podborska M, Mazanec R, Dusek L, Jarkovsky J, Bednarik J, Vohanka S, Srotova I. Anti-Müllerian hormone as an ovarian reserve marker in women with the most frequent muscular dystrophies. Medicine (Baltimore). 2020; 99(23):e20523. doi: 10.1097/MD.0000000000020523. PMID: 32502004**

This was the first study that extends findings of reduced ovarian reserve, as demonstrated by lower levels of anti-Müllerian hormone, to the general MD1 women population, i.e. not only those women with clinically clear fertility impairment, that undergoing in vitro fertilization. This was also the first study evaluating female fertility using AMH concentration in women with the other most frequent types of muscular dystrophy, i.e. in MD2, FSHD and cDMD.

Some muscular dystrophies may have a negative impact on fertility. In addition to symptomatic muscle involvement, other systems and organs are affected in muscular dystrophies, often including the reproductive and endocrine systems, which may negatively affect fertility. In men with myotonic dystrophy type 1 (MD1), reproductive problems due to a high prevalence of testicular atrophy and oligospermia or azoospermia are well-known manifestations of the disease. In MD1 women, fertility impairment is also considered highly

probable. But only limited and inconsistent data exist concerning the fertility of women patients with other muscular dystrophies, ie, myotonic dystrophy type 2 (MD2) or FSHD, or carriers of Duchenne muscular dystrophy mutations (cDMD). A decreased ovarian reserve is one of the factors assumed to be involved in fertility impairment. AMH (anti-Müllerian hormone) is considered the best measure of ovarian reserve.

The **purpose** of this study was to compare the ovarian reserve expressed as AMH values in women with the most frequent types of muscular dystrophy and those of healthy volunteers.

Methods: A total of 70 females with muscular dystrophies and 86 age-matched healthy controls were included in this prospective matched-case control study. The group of patients with muscular dystrophies consisted of 21 women with myotonic dystrophy type 1 (MD1), 25 women with myotonic dystrophy type 2 (MD2), 12 women with facioscapulohumeral muscular dystrophy (FSHD), and 12 female carriers of Duchenne muscular dystrophy mutations (cDMD). The inclusion criteria were: age between 18 and 44 years, presence of both ovaries, and regular menstrual cycles of between 25 and 35 days. The women had not used hormones or oral contraceptive pills within the three months before participation. In the patient group, a confirmed diagnosis of muscular dystrophy was also an inclusion criterion. Non-optimal compensation of thyroid disease was an exclusion criterion, but patients or controls with well-compensated thyroid disease, confirmed by normal thyroid-stimulating hormone (TSH) levels and free thyroxine (FT4) levels, were included in the study. An enzymatically amplified 2-site immunoassay was used to measure serum AMH level.

Results: The MD1 group was the only one to shows a significant decrease of AMH values (median 0.7ng/mL; range 0 – 4.9ng/mL) compared with age-matched healthy controls ($p<0.01$). Our study also extends these results to the general MD1 population (ie, not only those women with clinically clear fertility impairment reported previously in the literature [220]). Furthermore, the level ofAMH in our patients was very similar to that of the patients undergoing IVF in the previously reported study (median 0.7 ng/mL, range 0–4.9 in our study vs median 0.9 ng/mL, range 0.17–5.6 in the study cited), which confirms that decreased ovarian reserve is a general feature of MD1 female patients. AMH levels were similar between patients and controls in terms of females with MD2 $p=0.98$), FSHD ($p=0.55$), and cDMD ($p=0.60$). Apart from absolute AMH values, the number of patients/controls with AMH values outside the indicated reference range (age-related AMH nomogram) was also evaluated. In a similar fashion to absolute AMH values, the only significant differences were found between patients with MD1 and their healthy controls ($p<0.01$), while in all the other diagnoses of interest the proportion of abnormal AMH values was similar to the age-matched

control groups. Significant relationships between AMH and age were disclosed in all groups of patients and the group of healthy controls ($p<0.0001$). We also tested the relation of disease and AMH with age as a covariate, and disease still plays a statistically significant role for the AMH in the case of MD1 and MD2.

Conclusions: This study suggests decreased ovarian reserve in women with MD1, but not in MD2, FSHD, and cDMD. The results of this study add important considerations for MD1 patients. Women and family members should be informed about the possibility of prematurely decreasing ovarian function and the high risk of impaired fertility, thus providing an opportunity for realistic reproductive planning.

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Anti-Müllerian hormone as an ovarian reserve marker in women with the most frequent muscular dystrophies

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Abstract

Some muscular dystrophies may have a negative impact on fertility. A decreased ovarian reserve is 1 of the factors assumed to be involved in fertility impairment. AMH (anti-Müllerian hormone) is currently considered the best measure of ovarian reserve.

A total of 21 females with myotonic dystrophy type 1 (MD1), 25 females with myotonic dystrophy type 2 (MD2), 12 females with facioscapulohumeral muscular dystrophy (FSHD), 12 female carriers of Duchenne muscular dystrophy mutations (cDMD) and 86 age-matched healthy controls of reproductive age (range 18 – 44 years) were included in this case control study. An enzymatically amplified 2-site immunoassay was used to measure serum AMH level.

The MD1 group shows a significant decrease of AMH values (median 0.7 ng/mL; range 0 – 4.9 ng/mL) compared with age-matched healthy controls ($P < .01$). AMH levels were similar between patients and controls in terms of females with MD2 ($P = .98$), FSHD ($P = .55$) and cDMD ($P = .60$).

This study suggests decreased ovarian reserve in women with MD1, but not in MD2, FSHD and cDMD.

Abbreviations: AMH = anti-Müllerian hormone, cDMD = carriers of Duchenne muscular dystrophy mutations, FSH = follicle-stimulating hormone, FSHD = facioscapulohumeral muscular dystrophy, FT4 = free thyroxine, IVF = in vitro fertilization, LH = luteinizing hormone, MD1 = myotonic dystrophy type 1, MD2 = myotonic dystrophy type 2, MRC = medical research council, TSH = thyroid-stimulating hormone.

Keywords: anti-Mullerian hormone, fertility, muscular dystrophy, myotonic dystrophy, ovarian reserve

1. Introduction

Muscular dystrophies constitute a group of inherited neuromuscular diseases with progressive muscle involvement. In the Czech population, the most common forms are Duchenne and Becker's muscular dystrophy, myotonic dystrophy, facioscapulohumeral muscular dystrophy (FSHD) and limb-girdle muscular dystrophies. In addition to symptomatic muscle involvement, other systems and organs are affected in muscular dystrophies, often including the reproductive and endocrine systems, which may have a negative impact on fertility. In men with myotonic dystrophy type 1 (MD1), reproductive problems due to a high prevalence of testicular atrophy and oligospermia or azoospermia are well-known manifestations of the disease.[1] In MD1 women, fertility impairment is also considered highly probable.[2] To the best knowledge of the authors, only limited and inconsistent data exist concerning the fertility of women patients with other muscular dystrophies, ie, myotonic dystrophy type 2 (MD2) or FSHD, or carriers of Duchenne muscular dystrophy mutations (cDMD).

Decreased ovarian reserve is considered 1 of the most important factors in female fertility impairment.[3] Ovarian reserve may be assessed by measuring basal female sex hormones (follicle stimulating hormone [FSH], luteinizing hormone [LH], and estradiol), inhibin B, and anti-Müllerian hormone (AMH), and/or by antral follicle count. AMH is considered 1 of the most important markers of fertility in women.[4,5]

AMH is a glycoprotein produced by the gonads, specifically the granulosa cells of the ovarian follicles. AMH is secreted by the

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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granulosa cells in primary, secondary, pre-antral and early antral follicles, and the number of these follicles to grow appears to be related to the size of the resting primordial follicle pool.[6,7] AMH is therefore a useful endocrine marker and currently the best available measure of ovarian reserve.[7,8] The primary role of AMH is to inhibit the recruitment of follicles, thus preventing premature depletion of the follicle pool.[8] The dynamics of AMH levels change throughout life due the decline of the quantity and quality of the ovarian follicle pool.[9,10] Different initial sizes of the follicle pool and variations in the pace of follicle pool depletion between individuals mean that major differences in AMH levels are evident in women of the same chronological age.[11] Among other things AMH measurement is useful in prediction of a woman's future reproductive lifespan.[7,8]

The purpose of this study was to compare the ovarian reserve expressed as AMH values in women with the most frequent types of muscular dystrophy and those of healthy volunteers.

2. Methods

A total of 70 females with muscular dystrophies and 86 healthy controls were included in this prospective matched-case control study, carried out in the period between January 2017 and May 2018. The group of patients with muscular dystrophies consisted of 21 women with MD1, 25 women with MD2, 12 women with FSHD and 12 women with cDMD. The inclusion criteria were: age between 18 and 44 years, presence of both ovaries, and regular menstrual cycles of between 25 and 35 days. The women had not used hormones or oral contraceptive pills within the 3 months prior to participation. In the patient group, confirmed diagnosis of muscular dystrophy was also an inclusion criterion. Non-optimal compensation of thyroid disease was an exclusion criterion, but patients or controls with well-compensated thyroid disease, confirmed by normal thyroid-stimulating hormone (TSH) levels and free thyroxine (FT4) levels, were included in the study (Table 1). Patients were recruited from the national registry of muscular dystrophies and were investigated in 2 neuromuscular centres. The diagnosis of all patients recruited into the study was confirmed by means of molecular genetic testing (PCR, Southern blot, multiplex ligation-dependent probe amplification). Considering the different age distribution in particular diagnosis-related subgroups (Table 1), specific control groups were created for each patient subgroup to achieve optimal age-matching, using the propensity score method in R software with MatchIt package. Detailed data concerning these subgroups appear in Table 1. The content of the particular control subgroups was: 42 healthy controls to 21 women with MD1 (2:1 ratio), 25 healthy controls to 25 females with MD2 (1:1 ratio), 36 healthy controls to 12 females with FSHD (3:1 ratio) and 12 healthy controls to 12 carriers of Duchenne muscular dystrophy (1:1 ratio). The optimal ratio was set individually for each dataset on the basis of sufficient standardized difference between the groups analyzed after matching. All patients and controls were Caucasians. The study was approved by local ethics committee before the study began. Informed consent was obtained from all subjects.

AMH levels were measured in serum samples using the Beckman Coulter Access 2 immunoassay system. The Access AMH assay is a simultaneous 1-step immuno-enzymatic ("sandwich") assay. Its design parameters include a limit of detection of $\leq$0.02 ng/mL (0.14 pmol/L) and a Limit of Quantitation of $\leq$0.08 ng/mL (0.57 pmol/L). All blood samples

Table 1
Characteristics of study participants.

Variables	MD1 (n = 21)	MD1 control group (n = 42)	*P*-value*	MD2 (n = 25)	MD2 control group (n = 25)	*P*-value*	FSHD (n = 12)	FSHD control group (n = 36)	*P*-value*	cDMD (n = 12)	cDMD control group (n = 12)	*P*-value*
Age (yr)	36 (24– 44)	35 (24–44)	.94	36 (19–44)	36 (21–44)	.76	27.5 (18–44)	27.5 (20–44)	.97	41 (19–44)	40.5 (21–44)	.95
BMI (kg/m^2)	23.5 (17.8–44.5)	21.8 (17.6–34.7)	.37	21.6 (17.1–35.4)	22.1 (18.3–33.3)	.86	21.6 (15.2–27.0)	22.1 (18.5–34.2)	.27	25,5 (17.7–33.0)	22.6 (19.1–26.6)	.14
Age of onset (yr)	15 (0 – 30)	n.a.	n.a.	29 (17–ASX)	n.a.	n.a.	16 (10–30)	n.a.	n.a.	ASX	n.a.	n.a.
Disease duration (yr)	15 (4–32)	n.a.	n.a.	5 (0–20)	n.a.	n.a.	7 (0–25)	n.a.	n.a.	ASX	n.a.	n.a.
MRC (sum score)	157.3 (133.5–169.8)	n.a.	n.a.	163.8 (116–170)	n.a.	n.a.	161 (92.3–170)	n.a.	n.a.	170	n.a.	n.a.
FT4 serum levels (pmol/L)	15.3 (12.1–18.7)	15.4 (12.2–21.2)	.37	14.9 (13.2–21.9)	16.3 (12.6–21.5)	.68	15.6 (12.1–22)	16.1 ((12.2–21.5)	.78	14.2 (12.5–16.2)	15 (12.8–21.2)	.42
TSH serum levels (mU/L)	1.8 (0.8-3.9)	2.3 (0.8–3.4)	.50	1.6 (0.6–3.2)	1.9 ((0.7–3.4)	.31	1.9 (0.6–2.8)	2.0 (0.7–3.2)	.45	1.7 (0.9–3.1)	1.9 (1.1–3.5)	.64
Thyroid disease†	2 (9.5%)	3 (7.1%)	.74	8 (32%)	5 (20%)	.33	2 (16.7%)	3 (8.3%)	.41	1 (8.3%)	1 (8.3%)	1.00

Values are medians (range).
ASX = asymptomatic, BMI = body mass index, cDMD = carriers of Duchenne muscular dystrophy mutations, FSHD = facioscapulohumeral muscular dystrophy, FT4 = free thyroxine, MD1 = myotonic dystrophy type 1, MD2 = myotonic dystrophy type 2, MRC = medical research council, n.a. = not applicable.
* Mann-Whitney *U*-test in continuous variables or chi-square test for categorical variables.
† Absolute/relative frequency.

for the evaluation of AMH were examined in the same laboratory. The serum level of FT4 was also established in all patients and controls.

The Medical Research Council scale was used to assess the severity of muscle weakness. This scale evaluates the muscle strength of a total of 18 muscles (muscle groups), routinely using a scale ranging from 0 to 5 points for each muscle (group) for a total maximum of 170 points. Certain muscles groups were counted twice because of bilateral assessments.[12]

Body mass index was calculated from the weight and height established on initial examination.

The distribution of AMH, the outcomes and the covariates of interest are presented as median and range for continuous variables and the absolute/relative frequencies for categorical variables. Comparison of particular groups was performed by means of the Mann-Whitney *U* test with respect to non-normal distribution of the data. The Spearman correlation test was used for correlation analyses. The Chi-square test was employed to compare categorical data between the groups. We tested relation of each disease and AMH with age as covariate using general linear model. Statistical significance was considered as $P < .05$. Statistical analysis was performed using Statistica 12 software.

3. Results

Demographic and clinical data of all the patient subgroups and their controls are summarized in Table 1. No relevant differences emerged between patients with any diagnosis of interest and relevant control groups in terms of age, body mass index or history of thyroid disease. Any thyroid disease was well-compensated in all the subjects included, as documented by evaluation of FT4 serum levels, which was in normal range in all patients and controls. Patients with MD2 had shorter duration of the disease with respect to higher age of disease onset in this group, which is a feature typical of MD2 (compared with MD1). The clinical severity of the disease (expressed as medical research council sum score) showed highest variability in FSHD patients in particular (ranging from asymptomatic to moderate muscle impairment). The severity of disease in MD1 and MD2 was mostly mild, which might be anticipated with respect to the age of groups. All the carriers of Duchenne muscular dystrophy mutations were asymptomatic.

Table 2 summarizes the AMH levels in each of the patient subgroups and the comparison with relevant healthy controls. The MD1 group was the only 1 to show a significant decrease of AMH values compared with age-matched healthy controls. Apart from absolute AMH values, the number of patients/controls with AMH values outside the indicated reference range (age-related AMH nomogram)[13] was also evaluated. In similar fashion to absolute AMH values, the only significant differences were found between patients with MD1 and their healthy controls, while in all the other diagnoses of interest the proportion of abnormal AMH values was similar to the age-matched control groups.

The results of the relationship between AMH and age appear in Table 2. Significant relationships between AMH and age were disclosed in all groups of patients and in the group of healthy controls. We tested relation of disease and AMH with age as covariate and disease still plays statistically significant role for the AMH in the case of MD1 and MD2 ($P < .05$).

Table 2

AMH levels and relationship between AMH and age.

AMH (ng/mL)	MD1 (n = 21)	MD1 control group (n = 42)	*P*-value	MD2 (n = 25)	MD2 control group (n = 25)	*P*-value	FSHD (n = 12)	FSHD control group (n = 36)	*P*-value	cDMD (n = 12)	cDMD control group (n = 12)	*P*-value	Controls (n = 86)
Total AMH level [ng/mL]	0.7 (0–4.9)	2.7 (0–11.3)	<.01*	2.4 (0.1–7.4)	2.5 (0.2–7.1)	.98*	3.3 (0.3–7.4)	3.5 (0.5–16)	.55*	2.4 (0–10)	1.4 (0.5–5.2)	.60*	n.a.
AMH outside range [ng/mL] [13]													
Above norm	0	0	n.a.	0	0	n.a.	0	1	.56**	0	0	n.a.	n.a.
Below norm	10	6	<.01**	2	3	.64**	2	1	.09**	2	1	.54**	n.a.
Age	<0.0001***	n.a.	n.a.	<0.0001***	n.a.	n.a.	<0.0001***	n.a.	n.a.	0.0001***	n.a.	n.a.	<0.0001***

Values are medians (range).
AMH = anti-Müllerian hormone, cDMD = carriers of Duchenne muscular dystrophy mutations, FSHD = facioscapulohumeral muscular dystrophy, MD1 = myotonic dystrophy type 1, MD2 = myotonic dystrophy type 2, n.a. = not applicable.
* Mann-Whitney *U*-test.
** Chi-square test.
*** *P*-value, Spearman rank correlation coefficient.

4. Discussion

Fertility disorders are a frequent and increasing problem in the general population, affecting approximately 8% to 12% of reproductive-age couples worldwide.[14] Adequate ovarian reserve is 1 of the most important factors to impact upon female fertility. Several current studies have demonstrated that serum AMH concentration best represents the ovarian reserve and can thus be considered the most suitable predictor of female fertility.[4,5] This is supported by the number of studies showing a strong correlation between serum AMH levels and follicle count.[15,16] AMH has therefore come into widespread use in studies addressing reduced fertility in women.[17,18] About 10% of healthy controls in our study had low AMH levels, which nicely corresponds to the expected prevalence of fertility problems in the general fertile population mentioned above. AMH level changes throughout life, while inter-individual variability is wide due to differences in initial follicle pool capacities and the pace of follicle pool depletion.[7] Levels of AMH serum decline with increasing chronological age, and therefore age-related AMH nomograms, have been established by a number of studies.[10,13,19] The current study confirmed that AMH levels are inversely correlated with age in all groups of patients and controls.

The key finding here is that a decrease of AMH concentration occurred in females with type 1 myotonic dystrophy compared with the control group and the established normal range of AMH. This finding indicates a reduced ovarian reserve and the possibility of reduced fertility potential in women with MD1. Only few reports indicate a decrease of fertility in muscular dystrophies. Almost all of them concentrate on MD1. Based on these studies, fertility in women with MD1 appears to be impaired. Female patients with MD1 have decreased ovarian sensitivity, with reduced response to ovarian stimulation and less favourable outcomes for in vitro fertilization (IVF), suggesting poor ovarian condition.[2,20–22] Reduced ovarian reserve, as demonstrated by lower levels of AMH, was revealed in a recent study, to date the only 1 to determine AMH levels in MD1 females.[2] This study points out that women with MD1 undergoing IVF have significantly lower AMH compared with controls (also undergoing IVF for other reasons). Our study extends these results to the general MD1 population (ie, not only those women with clinically clear fertility impairment). Furthermore, the level of AMH in our patients was very similar to that of the patients undergoing IVF in the above-mentioned study (median 0.7 ng/mL, range 0–4.9 in our study vs median 0.9 ng/mL, range 0.17–5.6 in the study cited), which clearly confirms that decreased ovarian reserve is a general feature of MD1 female patients. Decreased ovarian reserve was also observed in another study, where the day-3 FSH, estradiol, antral follicle count and number of oocytes retrieved were lower in MD1 patients, although fertilization rate and embryo quality were similar when compared with women who had undergone IVF and intracytoplasmic sperm injection in response to male infertility.[22] Another authors report a higher number of poor-quality embryos and lower pregnancy rates in MD1 women.[21] There are also certain studies that suggest no differences in the pregnancy rate for MD1 females.[20,23] In summary, most of studies mentioned found decreased ovarian reserve in MD1 females, while others measured parameters resulted in different findings.

To the best of the authors' knowledge, this is the first study evaluating female fertility by means of AMH concentration in patients with the other most frequent types of muscular dystrophy, ie, in MD2, FSHD, and cDMD. No significant decrease of AMH levels was found in any of these patient groups when compared with age-matched healthy controls and the established normal range of AMH in the general population. No specific data are available on female fertility in MD2 and FSHD. The carriers of X-linked diseases, including Duchenne muscular dystrophy, have been used as a control group in a study with MD1 females; normal response to ovarian stimulation was found [21], which is fully in the line with the observations herein.

In addition to the clear dependence of AMH level on age mentioned above, various other factors may influence AMH concentration. Undiagnosed and untreated thyroid disease can be a cause of infertility, and anovulation is typically seen in women with thyroid hypofunction.[24] To exclude the influence of thyroid dysfunction on reproduction, this study measured the TSH and FT4 level in all the women involved. The concentration of TSH and FT4 in serum was normal in all patients and controls and thyroid dysfunction thus does not appear to represent a factor with potential significant influence on AMH levels.

Most studies maintain that AMH does not change significantly in the course of the menstrual cycle.[25] According to the automated Access AMH assay, AMH levels appear to be relatively stable across the menstrual cycle.[26] In the studies that created AMH nomograms, AMH measurement was also performed independently of the menstrual cycle.[13,19] For this reason, the authors did not perform blood collections for AMH testing at any specific phase of the menstrual cycle.

Several studies described the relationship between AMH and gonadotrophins. Elevated levels of AMH suppress FSH secretion[27] and also it was shown that AMH has a strong inhibitory effect on cyclic follicular recruitment in vivo by reducing the follicle sensitivity to FSH.[28] But on the other hand it was demonstrated a stimulatory effect of AMH on the expression of the FSH β-chain gene in gonadotrope-derived cell lines in pituitary with an increasing the secretion of FSH without affecting LH levels.[29] AMH also induces LH secretion by stimulating the activity of the hypothalamic Gonadotropin-releasing hormone (GnRH) neurons, which express AMH receptors.[30] However, it has been also documented, that GnRH lowers serum AMH levels and increase the gonadotrophins (FSH and LH).[31] So relationship between AMH and the hypothalamic–pituitary–gonadal axis is more complex, but shows the important role of AMH in the regulation of fertility by influencing the hypothalamic-pituitary function. Abnormalities of hypothalamic–pituitary–gonadal axis with secondary hypogonadism or combined form of primary and secondary hypogonadism have been reported in some MD1 patients.[32]

To the best of the authors' knowledge, this is the first study evaluating fertility by means of AMH concentration in patients with the most frequent types of muscular dystrophy and the first study to use AMH determination for other dystrophies beyond MD1. This is also the first study to evaluate fertility by means of AMH concentration in the general population of female MD1 patients (not limited to a selected population with clear fertility impairment).

The small sample of patients constitutes a weakness of this study, although the authors investigated almost all of the women of fertile age listed in the national registry. Further studies are therefore needed to confirm or question our findings. This study presents the partial results of an extensive female fertility study of those of who suffer from muscle dystrophies, presenting the ovarian reserve as 1 of the factors that reflects women's fertility.

MD1 is a complex disorder caused by the DNA expansion in myotonic dystrophy protein kinase gene. Expression of the mutated gene gives rise to an expanded repeat RNA that is retained in the nucleus and is directly toxic to cells in affected tissue. Although the mechanism of the deleterious effects of this expansion disease on the gonads is not known, it is possible that the expanded RNA also accumulates in ovarian cells and thus may have a negative impact on the ovarian function.[2] Although the MD2 is also an expansion disease like MD1 caused by the DNA expansion in cellular nucleic acid-binding protein gene, the expression of the mutated gene with expanded repeat RNA seems to be less pronounced in MD2 leading to a milder presentation of the multisystemic disorder with smaller number of affected tissues. MD2 also manifests often later at the end of the reproductive age of a woman, which could also be 1 of the reasons of normal AMH levels.

The results of this study add important considerations for MD1 patients. Women and family members should be informed about the possibility of prematurely decreasing ovarian function and high risk of impaired fertility, thus providing an opportunity for realistic reproductive planning.

Author contributions

O. Parmova was involved in literature review, recruitment and examination of patients, data collection, data interpretation, data analysis and prepared the first draft of the manuscript. M. Hulova and L. Mensova contributed to recruitment and examination of patients and controls, data collection and data interpretation. P. Stradalova and E. Kralickova contributed to data interpretation and analysis. M. Podborska contributed to collection and interpretation of blood samples (for the evaluation of anti-Müllerian hormone). L. Jurikova contributed to recruitment of patients. L. Dusek and J. Jarkovsky contributed to interpretation of data (statistical analysis). R. Mazanec contributed to data interpretation and reviewed/edited manuscript. I. Crha contributed to study design, data interpretation and reviewed/edited manuscript. E. Vlckova, J. Bednarik and S. Vohanka contributed to study design and data interpretation, to discussion and reviewed/edited manuscript. I. Srotova assumed overall responsibility for the study, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She contributed to study design, literature review, data collection, data interpretation, recruitment and examination of patients and controls and prepared the first draft of the manuscript. All authors approved the final manuscript.

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15.2. **Horáková M, Horák T, Parmová O, Bednařík J, Voháňka S. Quantitative myotonia assessment with a commercially available dynamometer in myotonic dystrophy types 1 and 2. Muscle Nerve. 2019; 59(4):431-435. doi: 10.1002/mus.26401. Epub 2019 Jan 9. PMID: 30575988**

This was the first study that demonstrated the commercially available dynamometer as a simple method for quantitative assessment of myotonia during routine examinations and as an outcome measure in clinical trials.

Myotonia is a cardinal symptom of myotonic disorders, including myotonic dystrophies and nondystrophic myotonias. Myotonia can vary from mild to severe and may constitute a substantial disability. In some cases exist inconsistencies in the assessment of myotonia between a history of myotonia reported by patients and the clinical evidence of the myotonic phenomenon.

The **objective** of this study was to develop a simple method for quantitative assessment of myotonia in patients with myotonic dystrophy type 1 and type 2 (MD1; MD2), to compare the myotonia severity, and to correlate this objective outcome with a subjective scale, the Myotonia Behaviour Scale (MBS). Relaxation time (RT) after maximum voluntary contraction is currently the variable most frequently employed in the assessment of myotonia.

Methods: A commercially available dynamometer was used for all measurements. The relaxation time after the voluntary contraction was measured in 20 patients with MD1, 25 patients with MD2, and 35 healthy controls. Relaxation time was measured from the dominant hand for all participants. Patients were asked to perform a contraction at a previously defined force, hold it for 3 s, and then release the grip as fast as possible. Three sets of measurements (trials) were performed with 10-min intervals of rest between trials. Each trial consisted of 6 voluntary contractions with an approximately 10-s rest period between each contraction.

Results: The average relaxation time was 0.17 s in controls, 2.96 s in patients with MD1, and 0.4 s in patients with MD2. The upper limit of normal, as well as the maximum in the control group, was 0.27 s. All MD1 patients exceeded this limit (the minimum in the MD1 group was 0.33 s). In the MD2 group, 13 patients (52%) were below this limit; nevertheless, only 5 of them reported having myotonia. The correlation between relaxation time and MBS score was significant, 0.627 in patients with MD1 and 0.581 in patients with MD2.

Conclusion: This method provides a valid and reliable quantitative measure of grip myotonia suitable as an outcome measure in clinical trials and as part of routine examinations to gather data on the natural history of myotonic disorders.

QUANTITATIVE MYOTONIA ASSESSMENT WITH A COMMERCIALLY AVAILABLE DYNAMOMETER IN MYOTONIC DYSTROPHY TYPES 1 AND 2

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ABSTRACT: *Introduction*: The objective of this study was to develop a simple method for quantitative assessment of myotonia in patients with myotonic dystrophy type 1 (DM1) and DM2, to compare the myotonia severity, and to correlate this objective outcome with a subjective scale, the Myotonia Behaviour Scale (MBS). *Methods*: A commercially available dynamometer was used for all measurements. The relaxation time after voluntary contraction was measured in 20 patients with DM1, 25 patients with DM2, and 35 healthy controls. *Results*: The average relaxation time was 0.17 s in controls, 2.96 s in patients with DM1, and 0.4 s in patients with DM2. The correlation between relaxation time and MBS score was significant, 0.627 in patients with DM1 and 0.581 in patients with DM2. *Discussion*: Our method provides a valid and reliable quantitative measure of grip myotonia suitable as an outcome measure in clinical trials and as part of routine examinations to gather data on the natural history of myotonic disorders. *Muscle Nerve* **XX:** 000–000, 2018.

Muscle Nerve **000**: 000–000, 2019

Myotonia is an abnormal delay in muscle relaxation after contraction. It is caused by increased excitability of the muscle fibers, leading to repetitive action potentials in response to stimulation. It is a cardinal symptom of myotonic disorders, including myotonic dystrophies and the nondystrophic myotonias. Although the most typical symptom of myotonia is difficulty in releasing a forceful handgrip, facial muscles, tongue, and other bulbar muscles may also be affected, resulting in problems with talking, chewing, and swallowing. Myotonia can vary from mild to severe and may constitute a substantial disability, leading to significant deterioration in quality of life.[1]

Development of a safe and effective drug treatment for myotonia that might be routinely employed remains the subject of current research. A Cochrane review[2] and its most recent amendment from 2009 concluded that trials reported as of 30 July 2009 were generally small and of poor quality. One aspect crucial to any clinical trial is reliable determination of the treatment effect; among the issues identified in the studies covered by the Cochrane review was the lack of a conclusive method for the quantitation of myotonia.

Relaxation time (RT) after maximum voluntary contraction is currently the variable most frequently employed in the assessment of myotonia. It may be measured by stopwatch or, more accurately, by specialized equipment and computerized protocols. Because repeated contraction and relaxation may temporarily improve myotonia (the "warm-up phenomenon"), it may influence results, depending on the duration and frequency of muscle contraction set for the test.

A computerized approach to the quantitation of myotonia in patients with myotonic dystrophy type 1 (DM1) employing a handgrip dynamometer was published in 2007.[3] The dynamometer produced an analog signal that was sent to a computer via an analog-to-digital transducer, and, subsequently, the RT was analyzed by customized software. This method was then used by the same authors to demonstrate the effect of mexiletine in a clinical trial[4] and tested in nondystrophic myotonias.[5] A later study (with lamotrigine) employed the Myotonia Behaviour Scale (MBS),[6] which consists of 6 statements from which the patient has to choose 1, ranging from asymptomatic (score 0) to severe (score 5) myotonia. This study used a stopwatch to measure the duration of myotonia.[7] In 2017, the authors of an open-label trial with ranolazine similarly chose stopwatch and subjective grading of stiffness severity by participants.[8] The computerized approach[3] requires special equipment that is not available in most centers, possibly explaining the choice of subjective questionnaires and less accurate measurement using stopwatches by other authors.

We sought to develop a simple method of quantitating myotonia using a commercially available dynamometer and to prove it suitable as an outcome measure in clinical trials and as part of routine examinations. Our objectives were to assess the reliability of the method, strength of correlation between RT and MBS, and differences of both RT and MBS between patients with DM1 and DM2.

MATERIALS AND METHODS

Study Participants. All study participants gave written informed consent, and all study procedures received approval

Abbreviations: C, healthy controls; DM, myotonic dystrophy; ICC, intraclass correlation coefficient; MBS, myotonia behavior scale; RT, relaxation time; RT_{100-10}, relaxation time from 100% to 10% of target force

Key words: muscle relaxation; muscle strength dynamometer; myotonia; myotonic dystrophy; outcome measure; warm-up

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from the institutional review board at the University Hospital, Brno. In total, 80 participants were enrolled, 20 patients with DM1, 25 patients with DM2, and 35 healthy controls (C). All patients were recruited from the Neuromuscular Centre of the University Hospital, Brno during routine visits in the period July 2017–March 2018. All patients were over 18 years, and all diagnoses had been genetically confirmed. Healthy controls were free of any known muscle disease and had no acute medical problems. Their recruitment was targeted at an equal distribution of age groups. All patients completed a Czech version of the MBS questionnaire.[9]

Measurements. The protocol of myotonia measurement was based on the approach described by Moxley *et al.*[3] in 2007. A commercially available handgrip dynamometer (DynX; MD Systems, Westerville, Ohio) was used for all measurements.

Patients were seated upright in a chair that permitted standardized arm positioning with the forearm in a neutral position and the wrist extended. Relaxation time after voluntary contraction was measured from the dominant hand for all participants. Patients were asked to perform a contraction at a previously defined force, hold it for 3 s, and then release the grip as fast as possible. They were asked to keep their fingers on the handles of the dynamometer throughout the measurement to eliminate the use of finger and wrist extensors to release grip. Three sets of measurements (trials) were performed with 10-min intervals of rest between trials. Each trial consisted of 6 voluntary contractions with an approximately 10-s rest period between each contraction.

The strength of voluntary contraction was set close to maximum, but target forces were established to ensure that each attempt was based on the same value. Prior to RT measurement, patients were encouraged to perform a maximal voluntary contraction in real-time mode, and the actual force after 3 s was recorded. The target force was then defined as 75% of the previously recorded maximal force. The 75% level (a figure selected after repeated testing among healthy volunteers) established the highest possible force that each participant was able to exert throughout. In the course of all attempts, patients were asked to exceed the target force for 3 s in visual response to an arrow on the display of dynamometer. Relaxation time was then automatically measured (by using a built-in feature of the dynamometer), from target force to 10% of target force.

Statistical Analysis. Data were analyzed in SPSS version 23 (IBM, Armonk, New York). Severity of myotonia was calculated as the mean RT from 100% to 10% of target force ($RT_{100–10}$) of the first squeeze in each trial. The same value was used to correlate the severity of myotonia with MBS score by using the Spearman correlation coefficient. Additional contractions were collected to analyze warm-up phenomenon, determined as a difference between the mean RT for the first squeeze and subsequent squeezes, and tested by using the Wilcoxon signed-rank test. Intraclass correlation coefficients (ICC; two-way random, average measures) were used to assess the inter-trial variability of the first squeezes in each group. Coefficients of variation (the ratio of standard deviation to the mean of 3 trials) were calculated to allow comparison of our simplified method to the original method because these variables had been used in previous studies.[3,5] In consideration of the lack of data normality, a Kruskal–Wallis test with a *post hoc* series of Mann–Whitney tests with Bonferroni corrections were employed to analyze the differences in RT and maximal force among DM1, DM2, and healthy controls. All other differences between DM1 and DM2 were assessed with Mann–Whitney tests. Data obtained from healthy controls were used to determine the upper limit of normal RT, calculated as a 0.95 quantile of the values.

Table 1. Comparison of basic characteristics, relaxation time, and maximal force in study participants.*

Variable	Controls	DM1	DM2
Age, y	46.8 (24, 89)	38.9 (24, 59)	53.1 (18, 74)
Sex, %	60 W, 40 M	70 W, 30 M	80 W, 20 M
Age of onset, y	na	21.1	35.9
Duration of disease, y	na	17.8	17.1
$RT_{100–10}$, s	0.17 (0.07, 0.27)	2.96 (0.33, 9.00)	0.40 (0.10, 1.80)
$RT_{100–10}$, SD	0.05	2.41	0.35
Maximal force, kg	21.9 (8.2, 37.1)	9.4 (3.3, 22.0)	15.0 (3.3, 41.3)
Maximal force, SD	7.7	2.4	8.7

DM, myotonic dystrophy; W, women; M, men; na, not applicable; $RT_{100–10}$, relaxation time from 100% to 10% of target force.

*Values are mean (minimum, maximum), except when indicated as SD.

RESULTS

Study Participants. Basic descriptive characteristics of the study participants are presented in Table 1. No age difference appeared between healthy controls and each group of patients, but a significant difference between DM1 and DM2 ($P < 0.0001$) emerged. Sex did not differ among groups. The mean age of onset differed significantly ($P < 0.0001$), whereas the mean duration of disease did not differ ($P = 0.451$).

Myotonia Quantitation. The results of $RT_{100–10}$ are presented in Table 1 and Figure 1. Significant differences were found among all groups. The upper limit of normal as well as the maximum in the control group was 0.27 s. All DM1 patients exceeded this limit (the minimum in DM1 group was 0.33 s). In the DM2 group, 13 patients (52%) were below this limit; nevertheless, only 5 of them reported having myotonia.

Intertrial Variability. The variability of $RT_{100–10}$ in each of the 3 trials is illustrated in Figure 2. The ICCs were 0.945 (DM1), 0.931 (DM2), and 0.437 (C). The intertrial variation coefficients of $RT_{100–10}$ were 22% (DM1), 29% (DM2), and 28% (C).

Myotonia Behaviour Scale. All but 4 patients (all of them DM1) completed the MBS questionnaire. The mean MBS scores were 2.6 (DM1) and 1.6 (DM2). The minimum (score 0) and maximum (score 4) were the same in both myotonia groups. The difference between MBS in the 2 groups was statistically significant ($P = 0.043$), even though Figure 3 clearly shows that patients with DM1 generally reported lower MBS than those with DM2 in relation to value of $RT_{100–10}$. For example, the mean $RT_{100–10}$ in

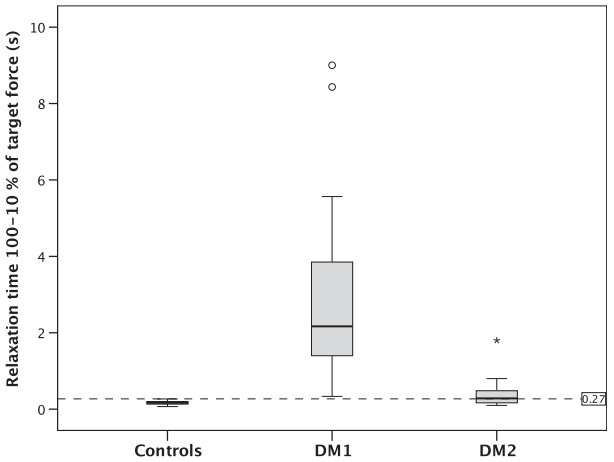

FIGURE 1. Relaxation time in healthy controls and patients with DM1 and DM2. The box plot indicates the 25th percentile, median, and 75th percentile. The circles represent outliers, and the asterisk represents extreme outliers. The dashed line represents the upper limit of normal calculated as a 0.95 quantile of the values in healthy controls. DM, myotonic dystrophy.

patients with an MBS score of 3 was 3.0 s in DM1 and 0.5 s in DM2 (both groups consisted of 7 patients). There was a significant correlation between MBS score and $RT_{100–10}$, with Spearman correlation coefficients of 0.627 (P = 0.001) in DM1 and 0.581 (P = 0.003) in DM2 (Fig. 3A,B).

Warm-up Phenomenon. An analysis of the warm-up phenomenon is presented in Figure 4. Differences in $RT_{100–10}$ were at their greatest between first and second voluntary contractions in both DM1 and DM2 (1.54-s decline in DM1, with $P < 0.0001$; 0.14-s decline in DM2, with $P = 0.02$). Although the differences between second and sixth voluntary contractions were still significant in DM1 (0.77 s, with $P = 0.004$), there was no further decline in DM2 (−0.02 s). Relaxation time from 100% to 10% of target force remained unchanged with consecutive contractions in the control group.

Maximal Force. The results for maximal force are presented in Table 1. Significant differences in maximal force emerged among all groups.

DISCUSSION

This study introduces a quantitative measure of hand-grip myotonia suitable both for clinical trials and routine examination. It exhibited low intertrial variability and significant correlation with a subjective scale assessing myotonia. More pronounced myotonia with more extensive warm-up phenomenon was demonstrated for the DM1 subgroup compared with the DM2 subgroup.

The main advantage of this method is the commercial availability of the dynamometer and the ease of postacquisition processing of data. Data are stored in a nonvolatile memory archive and can be transferred to a computer by using a USB connector and downloaded via automated software (provided freely by the manufacturer) as a simple spreadsheet of RT in relation to 10% steps in the target force. Data from the last test can be also directly displayed on the device.

The use of target force is also a considerable departure from the original method, which employed relaxation time after maximum voluntary contraction, a variable that might change from squeeze to squeeze. The force of maximal voluntary contraction might be affected by the motivation of the patient, particularly in consecutive measurements, so the results might be less consistent. This study examined RT in terms of a target force that remained the same throughout testing. In addition, the patients in the current study were asked to maintain grip for 3 s above the line of target force from which the RT was to be measured, thus eliminating any fluctuation in maximal force and also eliminating the requirement to choose a starting point for decline. Only 1 patient was unable to exert the required force repeatedly and, because

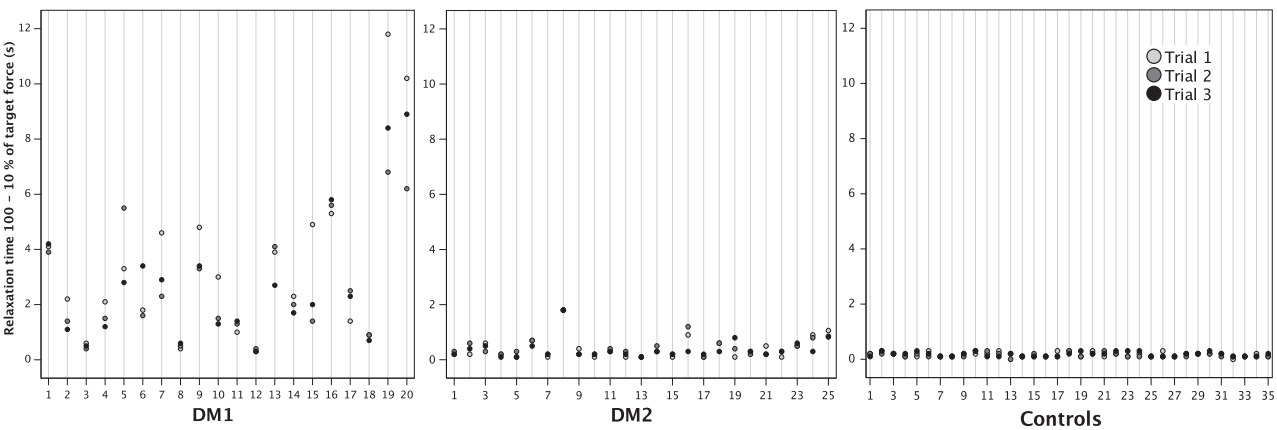

FIGURE 2. Intertrial variability of relaxation time of first squeezes in DM1, DM2, and healthy controls. Each number on the x-axis represents 1 participant from each group. DM, myotonic dystrophy.

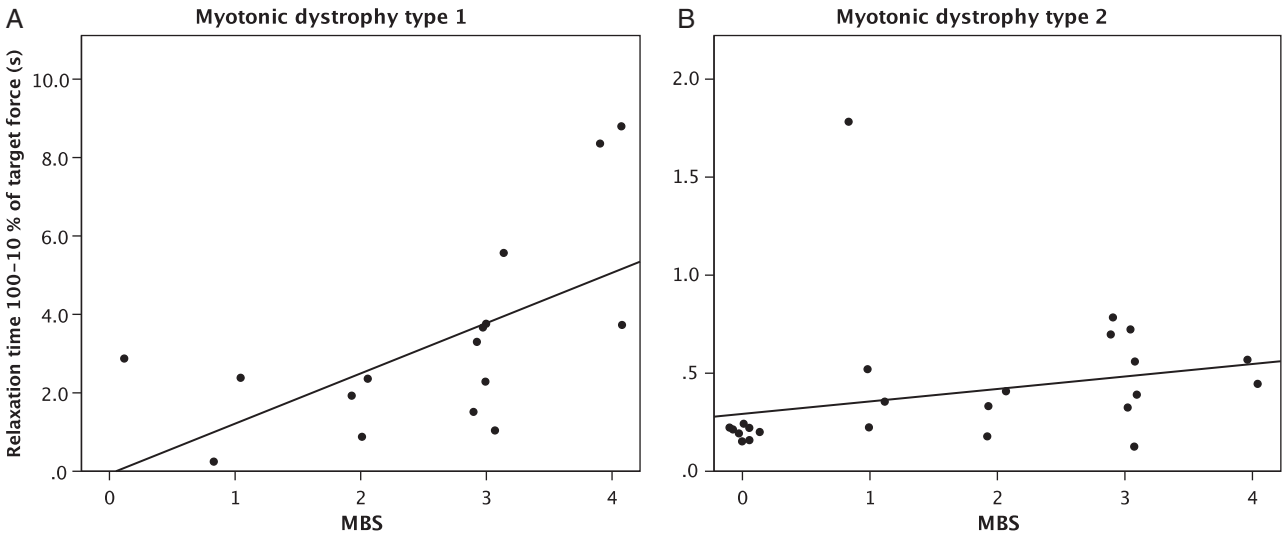

FIGURE 3. Correlation between relaxation time and MBS in patients with DM1 **(A)** and DM2 **(B)**. DM, myotonic dystrophy; MBS, Myotonia Behaviour Scale.

it occurred during the first trial, we simply reset the target force and repeated the measurement.

Even though we studied only intertrial variability, ICC for both DM1 and DM2 groups proved to be extremely high (0.945 and 0.931, respectively). The low ICC for healthy controls (0.437) can be explained by the very homogeneous values of $RT_{100–10}$ in this group. The coefficient of variation in this study was very similar to that obtained by the original method[3] (23.1% in controls and 33.2% in DM1 in the original method vs. 28% in controls and 22% in DM1 here), even though the patients were not fasting and a pegboard was not used to stabilize the arm as was the case in original study. Furthermore, the mean relaxation time from 90% to 5% of maximal force was quite similar (0.37 s in controls and 2.42 s in DM1) compared with our results for $RT_{100–10}$ (0.17 s in controls and 2.96 s in DM1). In the method that was employed here, the upper limit of normal was able to distinguish all DM1 patients, whereas, in the original method, 4 of the 25 patients with DM1 remained below the limit.

Simultaneous objective and subjective evaluation of myotonia severity also proved an advantage of this study. The correlation between $RT_{100–10}$ and subjective MBS was significant. Only 1 DM1 patient rated MBS at 0, even though his $RT_{100–10}$ was 2.8 s. The patient said explicitly that the current severity of his myotonia was nothing compared with that of a year ago. The study also demonstrated that MBS cannot be compared across different diseases because patients with DM1 generally reported lower MBS compared with those with DM2.

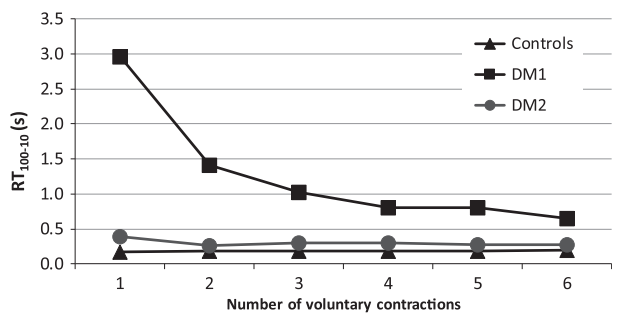

FIGURE 4. Warm-up phenomenon in healthy controls and patients with DM1 and DM2. DM, myotonic dystrophy; $RT_{100–10}$, relaxation time from 100% to 10% of target force.

The prevalence of DM2 in the Czech population is much higher than that of DM1.[10] This is in agreement with several other studies,[11,12] suggesting that DM2 might be underdiagnosed because the symptoms frequently occur in the elderly population. Myotonic dystrophy 2 is generally milder, with proximal weakness. This study confirmed that the average muscle force in patients with DM2 was significantly higher than that in patients with DM1 and demonstrated that the myotonia is less severe and the warm-up phenomenon less pronounced in DM2.

This study has some limitations. As previously discussed, a fixed target force was set throughout testing, which renders analysis of peak force and warm-up phenomenon of peak force impossible. All time values are rounded to one-tenth of 1 s, and the apparatus must be manually set to target force for each squeeze, which is not easy to accomplish when analyzing warm-up phenomenon (in the 10 s between squeezes). No group of nondystrophic myotonias was included, so it can only be assumed that the method described here may also be used for such a group.

In conclusion, the method detailed above provides a valid and reliable quantitative measure of grip myotonia in patients with DM1 and DM2. It is simple, requiring only a commercially available dynamometer and no other special equipment. Each trial takes about 1 min, but, after taking into consideration the

10-min intervals between the 3 trials, it takes about 35 min of a patient's time. We propose that it could be used as an outcome measure in clinical trials investigating drug treatments for myotonia. Its simplicity may also permit it to be used as a routine examination in gathering data on the natural history of myotonic disorders.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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15.3. **Parmová O, Vlčková E, Bednařík J, Voháňka S. Neuropathic pain component in patients with myotonic dystrophy type 2: a pilot study. Cesk Slov Neurol N 2019; 115(3): 322-332. doi: 10.14735/amcsnn2019322**

This pilot study supports the hypothesis and similar previously published findings of the possibility of thin-fiber dysfunction in patients with myotonic dystrophy type 2, and thus the possibility of the presence of a neuropathic component of pain in this patient group.

Patients with myotonic dystrophy may suffer from variable types of pain and some descriptors suggest the involvement of a possible neuropathic pain component in MD patients. The aim of the study was to evaluate the occurrence of neuropathic pain descriptors and sensory abnormalities in patients with myotonic dystrophy type 2 and to disclose the presence of some psychological abnormalities as potentially relevant psychological factors in chronic pain conditions.

Patients and methods: A group of 23 patients with MD2 (20 women, 3 men; mean age 53.5 ± 11.0 years, range 33–70 years) suffering from chronic pain and a group of 24 age- and gender-matched healthy controls (20 women, 4 men; mean age 51.9 ± 8.9 years, range 36–68 years) were examined using the PainDETECT questionnaire and the Neuropathic Pain Symptom Inventory questionnaire (NPSI), a comprehensive protocol of quantitative sensory testing (QST) and a battery of self-reported psychological tests. All examined patients reported unpleasant painful sensations of the limbs and torso lasting more than 3 months. The exclusion criteria were diabetes mellitus or impaired glucose tolerance, as well as the anamnestic occurrence of any other risk factors for polyneuropathy except mild hypothyroidism, which was well compensated in all cases.

Results: Based on the PainDETECT questionnaire, the presence of a neuropathic component of pain was evaluated as possible or probable in more than half of the patients. According to the NPSI questionnaire, the most frequently described spontaneous pain in patients with MD2 was squeezing. Very frequently, two-thirds of patients also described brief pain attacks of stabbing quality and abnormal sensations (pins and needles and/ or tingling) in the painful area. QST in lower legs showed significantly more frequent hypoesthesia for cold and hyperalgesia for mechanical pain stimuli and also a higher incidence of paradoxical heat sensation. Patients with MD2 showed significantly more frequent depression and pain catastrophizing.

Conclusion: The pain descriptors evaluated by PainDETECT and NPSI questionnaires, and sensory profile assessed by the QST protocol performed in this pilot study support the hypothesis that pain in MD2 patients probably has a neuropathic component.

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Neuropatická komponenta bolesti u pacientů s myotonickou dystrofií 2. typu: pilotní studie

Neuropathic pain component in patients with myotonic dystrophy type 2: a pilot study

Souhrn

Cíl: Bolest u myotonické dystrofie (MD) může mít variabilní charakter a některé deskriptory poukazují na možný podíl neuropatické komponenty bolesti u pacientů s MD. Cílem práce bylo zhodnocení výskytu deskriptorů neuropatické bolesti a senzitivních abnormit u pacientů s myotonickou dystrofií 2. typu (MD2) a posouzení některých psychologických faktorů významných v rozvoji chronické bolesti. *Soubor a metodika:* Skupina 23 pacientů s chronickou bolestí a geneticky potvrzenou MD2 a skupina 24 zdravých dobrovolníků obdobného věku a pohlaví byly vyšetřeny pomocí dotazníků PainDETECT a Neuropathic Pain Symptom Inventory (NPSI), komplexního protokolu kvantitativního testování senzitivity (quantitative sensory testing; QST) a baterie sebehodnotících psychologických testů. *Výsledky:* Dotazník PainDETECT poukázal na možnou či pravděpodobnou přítomnost neuropatické komponenty bolesti u více než poloviny pacientů. Podle dotazníku NPSI je spontánní bolest u MD2 pacientů nejčastěji svíravá, velmi časté jsou krátké záchvaty bodavé bolesti a téměř dvě třetiny pacientů vnímají brnění či mravenčení. QST prokázalo častý výskyt abnormit termického a algického čití, a to zejména na dolních končetinách. Pacienti s MD2 vykazovali také statisticky významně vyšší míru deprese a katastrofizace bolesti. *Závěr:* Deskriptory bolesti zachycené v rámci dotazníků PainDETECT a NPSI a senzitivní profil stanovený pomocí QST protokolu podporují v provedeném pilotním projektu hypotézu, že bolest u MD2 má pravděpodobně také neuropatickou komponentu.

Abstract

Aim: Patients with myotonic dystrophy (MD) may suffer from variable types of pain and some descriptors suggest the involvement of a possible neuropathic pain component in MD patients. The aim of the study was to evaluate the occurrence of neuropathic pain descriptors and sensory abnormalities in patients with myotonic dystrophy type 2 (MD2) and to disclose the presence of some psychological abnormalities as potentially relevant psychological factors in chronic pain conditions. *Patients and methods:* A group of 23 patients with MD2 suffering from chronic pain and a group of 24 age- and gender-matched healthy controls were examined using the PainDETECT questionnaire and the Neuropathic Pain Symptom Inventory questionnaire (NPSI), a comprehensive protocol of quantitative sensory testing (QST) and a battery of self-reported psychological tests. *Results:* Based on the PainDETECT questionnaire, the presence of a neuropathic component of pain was evaluated as possible or probable in more than half of the patients. According to the NPSI questionnaire, the most frequently described spontaneous pain in patients with MD2 was squeezing. Very frequently, two thirds of patients also described brief pain attacks of stabbing quality and abnormal sensations (pins and needles and/or tingling) in the painful area. QST in lower legs showed significantly more frequent hypoesthesia for cold and hyperalgesia for mechanical pain stimuli and also higher incidence of paradoxical heat sensation. Patients with MD2 showed significantly more frequent depression and pain catastrophizing. *Conclusion:* The pain descriptors evaluated by PainDETECT and NPSI questionnaires, and sensory profile assessed by the QST protocol performed in this pilot study support the hypothesis that pain in MD2 patients probably has a neuropathic component.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
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Úvod

Chronická bolest je celosvětově závažný zdravotní problém. Studie provedené v různých zemích dokazují, že chronickou bolestí trpí 10–30 % dospělé populace [1–3]. U nervosvalových chorob se chronická bolest vyskytuje dokonce u 60–80 % pacientů [4–6]. Intenzita a frekvence bolesti u progresivních neuromuskulárních chorob je podle provedených studií významně vyšší než v běžné populaci [7].

Myotonická dystrofie (MD) je nejčastější svalovou dystrofií v dospělém věku a druhou nejčastější svalovou dystrofií obecně. Jde o autozomálně dominantní multisystémové onemocnění s progresivní degenerací kosterních svalů. Hlavními projevy jsou progredující svalová slabost, myotonie a charakteristická multiorgánová postižení jako katarakta projevující se v mladším věku, poruchy srdečního rytmu a kardiomyopatie, kognitivní deficit, endokrinní poruchy, postižení gastrointestinálního traktu, únava, ospalost aj. Rozeznáváme dvě základní formy choroby s odlišným genetickým podkladem, a to myotonickou dystrofii typ 1 a myotonickou dystrofii typ 2 (MD2). Bolest u MD je častým a závažným příznakem choroby a její výskyt se pohybuje mezi 50–75 % [6,8–10]. Etiologie bolesti u MD není dosud spolehlivě objasněna a je pravděpodobně multifaktoriální. Jako jeden z multisystémových projevů u MD je popisováno i postižení periferních nervů [11,12].

Cílem této pilotní studie bylo zhodnotit možný podílu neuropatické komponenty bolesti u pacientů s MD2 prostřednictvím posouzení charakteristik bolesti a senzitivních abnormit (jejichž hodnocení patří k nejvýznamnějším a nejčastěji užívaným diagnostickým metodám ve výzkumu neuropatické bolesti) a posouzení některých psychologických charakteristik těchto pacientů jako potenciálně významných faktorů v rozvoji bolesti.

Soubor a metodika

V rámci prezentované studie jsme vyšetřili 23 pacientů s MD2 (potvrzenou molekulárně-geneticky v centru molekulární biologie a genové terapie FN Brno) a chronickou bolestí (20 žen; průměrný věk 53,5 ± 11,0 let, rozmezí 33–70 let) a skupinu 24 zdravých dobrovolníků obdobného věku a pohlaví (20 žen; průměrný věk 51,9 ± 8,9 let, rozmezí 36–68 let). Všichni vyšetření pacienti s MD2 byli chodící, z toho 22 pacientů (95,7 %) mělo známky svalové slabosti, která byla typicky lokalizována v kořenových svalech horních (HKK) a dolních (DKK) končetin, šíjových svalech nebo akrálních svalech DKK. Při hodnocení svalové síly pomocí Medical Research Council sum score (identická se svalovým testem dle Jandy) byla ve vyšetřovaném souboru průměrná hodnota skóre 163,7 ± 4,9 (maximální dosažitelné skóre při plné svalové síle ve všech hodnocených svalových skupinách dosahuje hodnoty 170 [13]), což odpovídá lehkému stupni svalového postižení, které je charakteristické pro MD2. Průměrný věk v době prvních projevů choroby byl 38,3 ± 11,9 let (rozmezí 15–65 let). Všichni vyšetření pacienti udávali nepříjemné bolestivé pocity končetin a trupu trvající déle než 3 měsíce. Detailní popis distribuce a intenzity bolesti je součástí výsledkové části práce. Osmnáct vyšetřených pacientů (78,3 %) mělo klinické projevy myotonie (poruchy svalové dekontrakce). V rámci standardního klinického vyšetření nevykazovali pacienti změny myotatických reflexů ani změny polohocitu, pohybocitu či vibrační nebo taktilní citlivosti jako známky postižení silných nervových vláken. Vylučujícím kritériem pro zařazení do souboru byl diabetes mellitus či porucha glukózové tolerance a také anamnestický výskyt jakýchkoli jiných rizikových faktorů polyneuropatií kromě mírné hypotyreózy, která byla přítomna u 6 z 23 pacientů (26,1 %) a byla ve všech případech medikamentózně kompenzována. Z ostatních sledovaných systémových příznaků MD byla přítomna katarakta (17/23 pacientů), poruchy srdečního rytmu (6/23 pacientů), postižení reprodukčních orgánů či infertilita (3/23 pacientů) a hyperhidróza (11/23 pacientů). Většina vyšetřených pacientů užívala dlouhodobě analgetika, a to nejčastěji nesteroidní antirevmatika (52,2 %), méně často tramadol (17,4 %) nebo kombinaci obojího (4,3 %). Část pacientů (26,1 %) navzdory popisované intenzitě bolestí žádná analgetika pravidelně neužívala. Současně žádný z pacientů neužíval antineuralgickou terapii, protože bolest u MD není standardně vnímána jako bolest neuropatická. Čtyřicet osm hodin před provedením studie neužili pacienti analgetika. V souboru zdravých dobrovolníků neměl ani jeden ze zařazených jedinců bolesti končetin či trupu ani známky polyneuropatie, svalové slabosti nebo myotonie.

Pacienti i dobrovolníci vyplnili dotazník PainDETECT a validovanou českou verzi dotazníku Neuropathic Pain Symptom Inventory (NPSI) [14–16]. Dotazník PainDETECT je primárně určen pro diagnostiku neuropatické bolesti a umožnuje stanovení míry pravděpodobnosti výskytu neuropatické komponenty bolesti u daného pacienta. Zohledňuje výskyt typických symptomů neuropatické bolesti, jejich intenzitu, průběh obtíží a jejich vyzařování do dalších částí těla. Při dosažení skóre 0–12 bodů je výskyt neuropatické komponenty nepravděpodobný. Skóre 13–18 bodů představuje nejednoznačný výsledek, kdy je přítomnost neuropatické komponenty bolesti možná. Při hodnotách skóre 19 a více je výskyt neuropatické komponenty bolesti u daného pacienta vysoce pravděpodobný (> 90 %). NPSI dotazník je zaměřen na popis charakteru bolesti vyšetřovaného v posledních 24 h. Intenzita bolesti je hodnocena pomoci škály Numeric Rating Scale (NRS) v rozsahu 0–10 bodů, kde „0" představuje „žádnou bolest" a „10" znamená „nejhorší představitelnou bolest".

Dále jsme u pacientů a dobrovolníků podrobně vyšetřili senzitivní profil s použitím české verze komplexního protokolu kvantitativního testování senzitivity (Quantitative Sensory Testing; QST) zavedeného německou pracovní skupinou pro výzkum neuropatické bolesti (Der Deutsche Forschungsverbund Neuropathischer Schmerz [DFNS], The German Research Network on Neuropathic Pain) [17,18]. QST je standardizovaná metoda k posouzení somatosenzitivních funkcí kvantifikací percepce široké škály senzitivních a algických modalit [19]. QST protokol reflektuje funkci silných (A-beta) i tenkých nervových vláken (A-delta i C) a patří mezi klíčové metody v diagnostice neuropatické bolesti. Vyšetření jsme provedli na HKK a DKK, a to vždy jednostranně na končetině, kde pacienti udávali větší bolesti. Vyhodnotili jsme senzitivní prahy (tj. nejnižší intenzitu dané modality, jež u vyšetřovaného subjektu vyvolá percepci podnětu) a prahy algické (tj. nejnižší intenzitu dané modality, která u vyšetřovaného vede k vyvolání bolestivého vjemu). U všech vyšetřených pacientů i dobrovolníků jsme v rámci QST protokolu vyšetřili senzitivní práh pro teplo (warm detection threshold), chlad (cold detection threshold) a také tzv. neutrální teplotní rozsah (thermal sensory limen), tedy teplotní rozmezí, v němž pacient vnímá teplotu jako neutrální. Hodnoceny byly dále vibrační čití (vibration detection threshold), senzitivní práh pro mechanickou kožní citlivost (mechanical detection threshold), algický práh pro ostrou mechanicky vyvolanou bolest (mechanical pain threshold) a hlubokou tlakovou

bolest (pressure pain threshold; PPT), senzitivitu pro ostrou mechanicky vyvolanou bolest (mechanical pain sensitivity), časovou sumaci ostrých mechanicky vyvolaných bolestivých podnětů hodnocenou pomocí tzv. wind-up ratio (WUR), termoalgický práh pro teplo (heat pain threshold) a chlad (cold pain threshold), výskyt tzv. paradoxního vnímání chladu jako tepla (paradoxical heat sensation) a mechanickou dynamickou alodyniiPC.

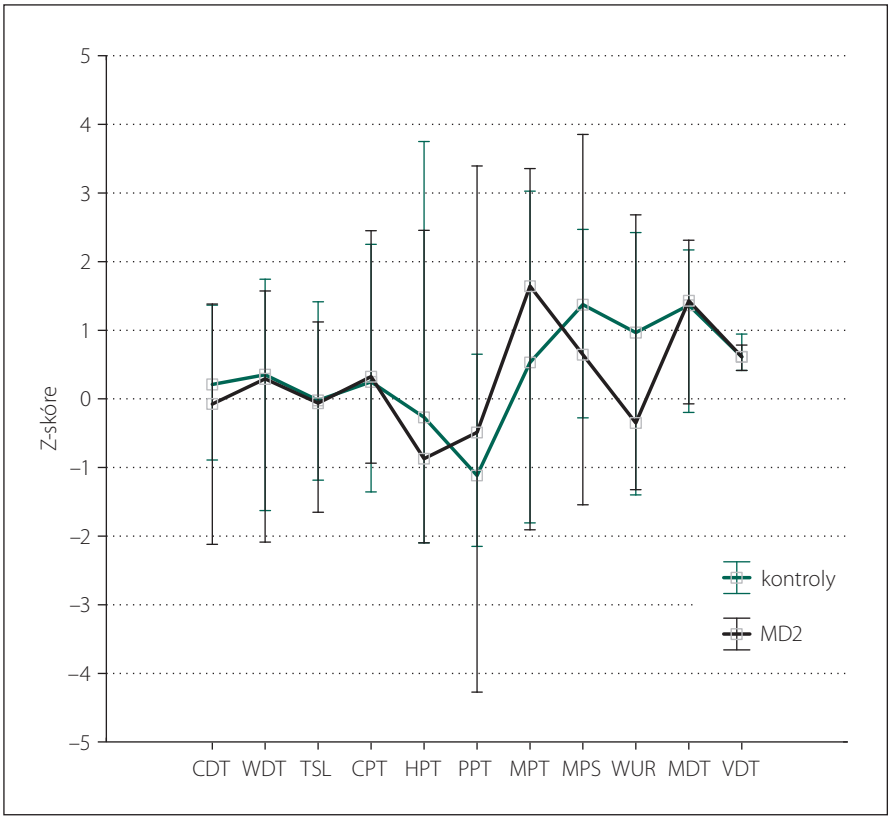
Stanovení těchto modalit umožňuje vytvořit tzv. senzitivní profil poskytující komplexní přehled o senzitivní percepci u daného pacienta.

Všichni pacienti a zdravé kontroly také vyplnili baterii sebehodnotících psychologických testů. Ke zhodnocení příznaků deprese byl použit dotazník Beck Depression Inventory (BDI) [20]. Ke zhodnocení katastrofizace bolesti byla použita škála Pain Catastrophizing Scale (PCS) [21].

Statistická analýza

Statistické výpočty byly provedeny pomocí softwaru Microsoft Excel (Microsoft Corporation, Redmont, WA, USA) a programu Statistica 12 (StatSoft s.r.o., Praha, Česká republika). Data získaná z dotazníků PainDETECT, NPSI, BDI a PCS byla normálně distribuována. Pro jejich srovnání mezi pacienty a kontrolami byl použit nepárový t-test, ke zviditelnění rozložení hodnot byly použity průměry a směrodatné odchylky. Data získaná z měřených charakteristik QST nevykazovala normální distribuci, pro srovnání jednotlivých parametrů QST mezi kontrolní skupinou a skupinou pacientů byl použit Mann-Whitneyův U Test a ke zviditelnění rozložení hodnot byly použity mediány a percentily. Vedle absolutních hodnot prahů vyjádřených v původních měrných jednotkách (°C, kPa, mN apod.) byly jednotlivé QST parametry vyjádřeny také formou tzv. Z-skóre, tedy počtu směrodatných odchylek od průměrné hodnoty prahu v příslušné věkové kategorii publikovaného normativního souboru (obr. 1,2). Kladné hodnoty Z-skóre přitom představují zvýšenou citlivost pro danou modalitu, záporné hodnoty naopak citlivost sníženou.

Kategoriální data jsou znázorněna pomocí absolutních (relativních) četností. Pro srovnání kategoriálních dat (frekvence výskytu abnormit typu ano/ne) mezi skupinou zdravých kontrol a skupinou pacientů byl použit chí-kvadrát test. Pro korelaci mezi celkovým počtem QST abnormit a sumárním NPSI skóre byl použit Pearsonův korelační koeficient.



Obr. 1. Kvantitativní testování senzitivity na horních končetinách: Z-skóre.
Data jsou prezentována jako medián (bod) a rozsah neodlehlých hodnot (whisker). Šipka ukazuje parametry, jejichž hodnoty vykazují statisticky významné rozdíly mezi kontrolní skupinou a pacienty s MD2 (s uvedením hodnoty statistické významnosti).

CDT – senzitivní práh pro chlad; CPT – termoalgický práh pro chlad; HPT – termoalgický práh pro teplo; MD2 – myotonická dystrofie 2. typu; MDT – senzitivní práh pro mechanickou kožní citlivost; MPS – senzitivita pro ostrou, mechanicky vyvolanou bolest; MPT – algický práh pro ostrou, mechanicky vyvolanou bolest; PPT – algický práh pro hlubokou tlakovou bolest; TSL – teplotní rozsah, vnímaný jako neutrální; VDT – senzitivní práh pro vibrační čití; WDT – senzitivní práh pro teplo; WUR – časová sumace ostrých mechanicky vyvolaných bolestivých podnětů

Fig. 1. Quantitative sensory testing of the upper limb: Z-score.
The data are presented as a median (point) and a non-outlier range (whisker). The arrow shows parameters with statistically significant differences between the control group and MD2 patients (indicating a statistically significant value).

CDT – cold detection threshold; CPT – cold pain threshold; HPT – heat pain threshold; MD2 – myotonic dystrophy type 2; MDT – mechanical detection threshold; MPS – mechanical pain sensitivity; MPT – mechanical pain threshold; PPT – pressure pain threshold; TSL – thermal sensory limen; VDT – vibration detection threshold; WDT – warm detection threshold; WUR – wind-up ratio

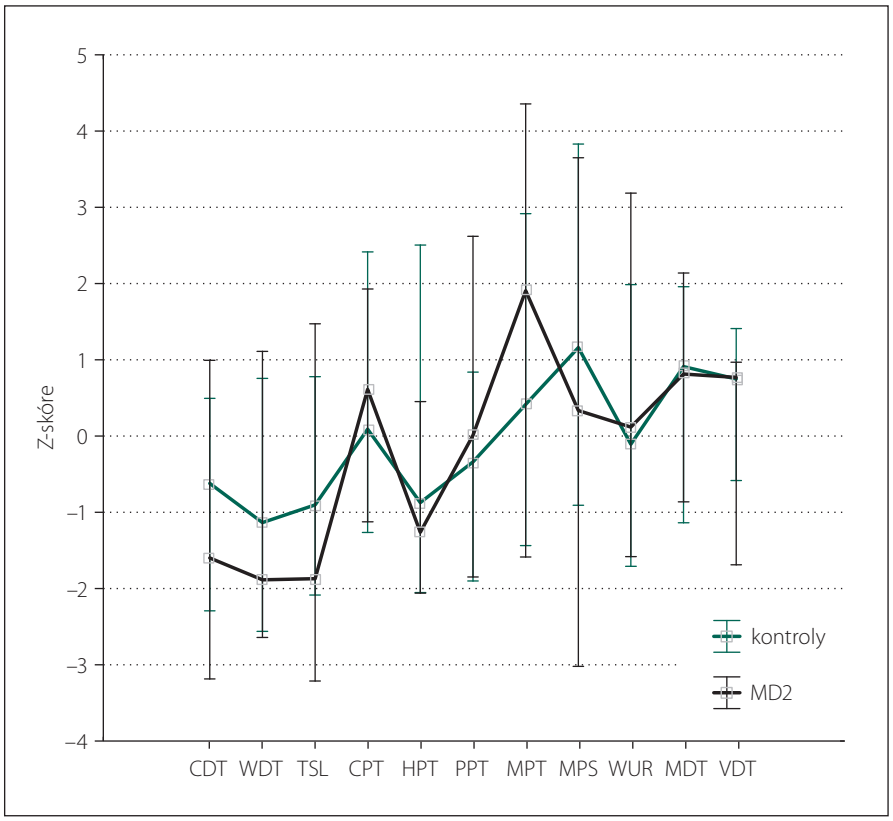
Výsledky

Charakteristika bolesti

Všichni pacienti udávali výskyt bolestí na DKK, a to distálně a ve více než 90 % případů současně proximálně v oblasti stehen. Téměř dvě třetiny pacientů měly bolesti i na HKK, a to častěji proximálně v oblasti paží (tab. 1). Většinou se jednalo o bolest symetrickou. Bolest byla nejčastěji vyvolána fyzickou aktivitou a/nebo chladem. Klidové bolesti vykazovala více než polovina pacientů. Průměrná intenzita bolesti udávaná pacienty při základním anamnestickém vyšetření byla dle NRS škály 5,2 ± 1,3.

Vyhodnocení dotazníku PainDETECT

Dotazník PainDETECT prokázal možnou nebo pravděpodobnou přítomnost neuropatické komponenty bolesti u více než poloviny pacientů s MD2 (tab. 2). Nejintenzivnější



Obr. 2. Kvantitativní testování senzitivity na dolních končetinách: Z-skóre.
Data jsou prezentována jako medián (bod) a rozsah neodlehlých hodnot (whisker). Šipka ukazuje parametry, jejichž hodnoty vykazují statisticky významné rozdíly mezi kontrolní skupinou a MD2 pacienty (s uvedením hodnoty statistické významnosti).
CDT – senzitivní práh pro chlad; CPT – termoalgický práh pro chlad; HPT – termoalgický práh pro teplo; MD2 – myotonická dystrofie 2. typu; MDT – senzitivní práh pro mechanickou kožní citlivost; MPS – senzitivita pro ostrou, mechanicky vyvolanou bolest; MPT – algický práh pro ostrou, mechanicky vyvolanou bolest; PPT – algický práh pro hlubokou tlakovou bolest; TSL – teplotní rozsah, vnímaný jako neutrální; VDT – senzitivní práh pro vibrační čití; WDT – senzitivní práh pro teplo; WUR – časová sumace ostrých mechanicky vyvolaných bolestivých podnětů

Fig. 2. Quantitative sensory testing of the lower limb: Z-score.
The data are presented as a median (point) and a non-outlier range (whisker). The arrow shows parameters with statistically significant differences between the control group and MD2 patients (indicating a statistically significant value).
CDT – cold detection threshold; CPT – cold pain threshold; HPT – heat pain threshold; MD2 – myotonic dystrophy type 2; MDT – mechanical detection threshold; MPS – mechanical pain sensitivity; MPT – mechanical pain threshold; PPT – pressure pain threshold; TSL – thermal sensory limen; VDT – vibration detection threshold; WDT – warm detection threshold; WUR – wind-up ratio

Tab. 1. Charakteristiky bolesti u pacientů s MD2.

Charakteristiky bolesti	Pacienti s MD2 s bolestí (n = 23)[1]
lokalizace bolesti	
HKK proximálně (paže)	14 (60,9 %)
HKK distálně (předloktí, ruce)	13 (56,5 %)
DKK proximálně (stehna)	21 (91,3 %)
DKK distálně (lýtka, nohy)	23 (100 %)
faktory vyvolávající/zhoršující bolest	
chlad	15 (65,2 %)
teplo	3 (13,0 %)
fyzická aktivita	17 (73,9 %)
klidové bolesti	13 (56,5 %)

[1] Hodnoty jsou uvedeny jako absolutní (relativní) frekvence.
DKK – dolní končetiny; HKK – horní končetiny; MD2 – myotonická dystrofie 2. typu

bolesti byly lokalizovány ve stehnech a lýtkách, méně pak v chodidlech. Průměrná intenzita bolesti dle NRS škály tohoto dotazníku dosahovala hodnot 5,4 ± 1,3 (tab. 2).

Vyhodnocení dotazníku NPSI

Dotazník NPSI, vytvořený primárně za účelem detailního popisu charakteru bolesti, prokázal alespoň jeden z deskriptorů typických pro neuropatickou bolest s jedinou výjimkou u všech vyšetřovaných pacientů s MD2. Většina pacientů popisovala bolesti spontánní chronické (87 % pacientů) a současně krátké záchvatovité bolesti (82,6 % pacientů). Spontánní bolest byla nejčastěji svíravá. Méně častá byla bolest vyvolaná, i když i tu uvádělo až 65,2 % pacientů. Nejčastěji byly bolesti u pacientů vyvolané či zhoršené tlakem (43,5 %) nebo kontaktem s chladem či teplem (39,1 %). Abnormální pocity jako brnění a mravenčení uvádělo 78,3 % pacientů. Průměrná intenzita udávané bolesti v jednotlivých položkách byla střední (NRS 5,2 až 6,4) (tab. 3). Jedno z derivovaných skóre české verze dotazníku (tzv. $NPSI_{cz-D}$ skóre vytvořené autory na podkladě diskriminační analýzy [15]) umožňuje i diskriminaci pacientů s neuropatickou a nociceptivní bolestí (i když k tomuto účelu nebyl dotazník primárně vytvořen). V našem souboru byla při použití tohoto skóre bolest klasifikována jako neuropatická u 22 pacientů (95,7 %) a nociceptivní u 1 pacienta (4,3 %), a resp. jako periferní neuropatická u 20 pacientů (87,0 %) a spontánní nociceptivní u 3 pacientů (13 %).

Vyhodnocení QST protokolu

Kvantitativní testování senzitivity prokázalo na HKK u pacientů s MD2 oproti zdravým kontrolám signifikantně častější hyperalgezii pro mechanické algické podněty a sníženou časovou sumaci mechanických algických podnětů (tab. 4 a obr. 1). Rozdíl druhého ze jmenovaných parametrů byl však pravděpodobně podmíněn spíše abnormálním zvýšením jeho hodnot u některých jedinců

v souboru zdravých kontrol. Na DKK nebyly rozdíly časové sumace bolestivých podnětů mezi oběma skupinami významně odlišné, u pacientů s MD2 jsme zde však zachytili významně častější hypestézii pro chlad (a to zejména při relativním vyjádření hodnot ve vztahu k věkově stratifikovaným datům (obr. 2) a hraničně i při hodnocení absolutních hodnot prahů – tab. 5). Významně častější byla u pacientů s MD2 také hyperalgezie pro mechanické algické podněty a výskyt paradoxního vnímání chladných podnětů jako teplých či horkých (tab. 5 a obr. 2). Při vyjádření individuálních hodnot jednotlivých parametrů ve vztahu k věkově stratifikovaným normativním datům (formou tzv. Z-skóre) byla na DKK patrná také signifikantní hypestezie pro teplo: abnormální termický práh pro teplo byl prokázán u 11 z 23 vyšetřených pacientů s MD2. Rozdíly absolutních hodnoty termických prahů pro teplo mezi MD2 pacienty a zdravými kontrolami však nedosáhly statistické významnosti, pravděpodobně z důvodu určitých malých rozdílů ve věkové distribuci pacientů mezi oběma skupinami a menšího počtu jedinců v obou skupinách (tab. 5). Dále byl patrný trend k širšímu teplotnímu rozsahu, v němž pacienti vnímali tepelně neutrální vjem. Ani rozdíly tohoto parametru mezi zdravými kontrolami a pacienty s MD2 však nedosáhly statistické významnosti (tab. 5 a obr. 2).

Celkový počet QST abnormit na HKK nebyl u pacientů s MD2 významně odlišný ve srovnání s kontrolní skupinou ($p = 0,76$). Tento rozdíl však byl velmi vysoce významný na DKK, kde celkový počet QST abnormit u pacientů s MD2 více než dvojnásobně přesáhl počet abnormit zachycených ve skupině zdravých kontrol ($p < 0,001$, data detailně neuvedena).

Vyhodnocení psychologických dotazníků

V sebehodnotících psychologických dotaznících vykazovali pacienti s bolestí při MD2 statisticky významně vyšší míru deprese a katastrofizace bolesti (tab. 6).

Diskuze

Bolest u MD je poměrně častým klinickým příznakem, mechanizmus jejího vzniku však není přesně znám a je pravděpodobně multifaktoriální. Není také jasné, proč u některých MD pacientů dojde k rozvoji bolesti a u jiných ne nebo proč bolest často vzniká ve stadiu onemocnění, kdy ještě nedošlo ke klinicky manifestnímu postižení svalového systému [22].

Tab. 2. Hodnoty jednotlivých položek dotazníku PainDETECT u pacientů s MD2 s bolestí.

Parametr	Pacienti s MD2 s bolestí (n = 23)	
	Počet pacientů[1]	Intenzita bolesti[2]
aktuální intenzita bolesti		4,0 (2,1)[4]
největší intenzita bolesti během minulých 4 týdnů		7,8 (1,6)[4]
průměrná intenzita bolesti během minulých 4 týdnů		5,4 (1,3)[4]
lokalizace největší bolesti:		
stehna	10 (43,5 %)	
lýtka	9 (39,1 %)	
chodidla	4 (17,4 %)	
vyzařování bolesti		
ano	10 (43,5 %)	
ne	13 (56,5 %)	
průběh bolesti:		
trvalá bolest s mírnými výkyvy	2 (8,7 %)	
trvalá bolest s občasnými záchvaty silné bolesti	6 (26,1 %)	
záchvaty silné bolesti, mezi nimi bez bolesti	14 (60,9 %)	
časté záchvaty silné bolesti, mezi nimi trvalá bolest	1 (4,3 %)	
charakter bolesti:		
pálivá bolest	15 (65,2 %)	2,3 (0,9)[5]
pocit brnění, šimrání, mravenčení	13 (56,5 %)	3,2 (1,5)[5]
bolest vyvolaná lehkým pohyblivým dotekem	5 (21,7 %)	1,6 (0,8)[5]
vystřelující záchvaty silné bolesti	11 (47,8 %)	2,8 (0,9)[5]
bolest vyvolaná chladem nebo teplem	16 (69,6 %)	3,6 (1,1)[5]
pocit znecitlivění	15 (65,2 %)	2,5 (0,7)[5]
bolest vyvolaná lehkým stálým tlakem	16 (69,6 %)	3,1 (0,9)[5]
celkové PainDETECT skóre[3]		
neuropatická komponenta bolesti je nepravděpodobná	11 (47,8 %)	
neuropatická komponenta bolesti může být přítomna	7 (30,4 %)	
neuropatická komponenta bolesti je pravděpodobná	5 (21,7 %)	

[1] Hodnoty jsou uvedeny jako absolutní (relativní) frekvence.

[2] Průměry (směrodatné odchylky) nenulových hodnot daného parametru.

[3] Vypočteno z otázek zaměřených na vyzařování bolesti, její průběh a charakter (v souladu s originální verzí dotazníku dle Freynhagena [16]).

[4] Hodnoceno pomocí NRS škály v rozsahu 0–10 bodů.

[5] Hodnoceno pomocí 6bodové verbální škály bolesti, každému verbálnímu deskriptoru intenzity je přidělena určitá číselná hodnota (vůbec ne = 0; takřka vůbec = 1; málo = 2; středně = 3; silně = 4; velmi silně = 5).

MD2 – myotonická dystrofie 2. typu

Jednou z možných hypotéz vzniku bolesti u MD může být například abnormální zátěž pohybového aparátu v důsledku svalové dysbalance při oslabení některých svalových skupin nebo při myotonii hlubokých svalů, kdy dlouhodobě zvýšený tonus hlubokého svalstva vyčerpává svaly této skupiny i jejich antagonisty [6]. Dlouhodobá kontrakce svalu

Tab. 3. Hodnoty jednotlivých položek NPSI dotazníku, celkového NPSI skóre a užívaných dílčích NPSI škál u MD2 pacientů s bolestí.

Parametr	Pacienti s MD2 s bolestí (n = 23)	
	Počet pacientů[1]	Intenzita bolesti (NRS)[2]
Q1: spontánní pálivá bolest	10 (43,5 %)	5,3 (2,7)
Q2: spontánní svíravá bolest	13 (56,5 %)	5,8 (2,6)
Q3: spontánní tlaková bolest	11 (47,8 %)	5,5 (2,9)
Q4: počet hodin se spontánní bolestí / 24 h		
< 1	7 (30,4 %)	
1–3	3 (13 %)	
4–7	2 (8,7 %)	
8–12	6 (26,1 %)	
neustále	5 (21,7 %)	
Q4: 1 a více hod se spontánní bolesti / 24 h	16 (69,6 %)	
Q5: krátké záchvaty bolesti jako elektrické šoky	7 (30,4 %)	5,6 (2,5)
Q6: krátké záchvaty bodavé bolesti	16 (69,6 %)	5,6 (2,6)
Q7: počet krátkých záchvatu bolesti / 24 h		
žádné	4 (17,4 %)	
1–5	10 (43,5 %)	
6–10	4 (17,4 %)	
11–20	1 (4,3 %)	
> 20	4 (17,4 %)	
Q7: 1 a více krátkých záchvatů bolesti / 24 h	19 (82,6 %)	
Q8: provokace/zhoršení bolesti dotykem	6 (26,1 %)	5,2 (2,5)
Q9: provokace/zhoršení bolesti tlakem	10 (43,5 %)	6,0 (3,0)
Q10: provokace/zhoršení bolesti chladem	9 (39,1 %)	6,4 (2,3)
Q11: mravenčení	15 (65,2 %)	6,3 (3,2)
Q12: brnění	15 (65,2 %)	6,1 (3,0)
trvalá bolest (Q1, Q2, Q3)[3]	20 (87,0 %)	5,5 (2,4)
záchvatovitá bolest (Q5, Q6)[3]	19 (82,6 %)	5,3 (2,7)
vyvolaná bolest (Q8, Q9, Q10)[3]	15 (65,2 %)	5,6 (2,6)
parestezie/dysestezie (Q11, Q12)[3]	18 (78,3 %)	5,9 (3,0)
celkové NPSI skóre[4]	22 (95,7 %)	29,5 (21,8)

[1] Hodnoty jsou uvedeny jako absolutní (relativní) frekvence.
[2] Vypočteno jako průměry (směrodatné odchylky) z nenulových hodnot daného parametru.
[3] Dílčí NPSI škály jsou vypočtené jako součet relevantních položek (uvedených v závorce).
[4] Celkové NPSI skóre je vypočteno jako součet položek Q1–Q3, Q5–Q6 a Q8–Q12 a dosahuje hodnot v rozmezí 0–100.
MD2 – myotonická dystrofie 2. typu; NPSI – Neuropathic Pain Symptom Inventory; NRS – Numeric Rating Scale

při myotonii může vést i k hypoperfuzi, vyplavení laktátu, poklesu hodnoty pH a uvolnění dalších látek, které mohou provokovat bolest, jako jsou bradykinin, adenosintrifosfát a ionty vodíku [20]. Na vzniku bolesti by se tak dle této hypotézy mohly podílet také změny, které přímo souvisejí s patofyziologickým řetězcem této choroby v rámci její multisystémové manifestace, kdy akumulace expandované transkribované ribonukleové kyseliny (RNA) poškozuje buněčné procesy a ovlivňuje sestřih RNA dalších desítek genů [24]. Důsledkem tohoto patofyziologického řetězce může být i zvýšení nocicepce. Všechny zmiňované mechanizmy jsou však spíše hypotetické a jednoznačný průkaz jejich významu v patofyziologii bolesti u MD není dosud k dispozici.

Charakter bolestí u pacientů s MD může být velmi variabilní. Při použití jednoho z nejčastěji užívaných dotazníků zaměřených na deskriptory bolesti (McGill Pain Questionnaire) udávali pacienti s MD v jedné z publikovaných studií bolest trhavou (škubavou), tupou, bodavou, tíživou, křečovitou, vyčerpávající nebo bolest charakteru nepříjemných pocitů ve svalech, jako je napětí, citlivost [10]. Některé ze zmíněných deskriptorů ukazují na možnou neuropatickou komponentu bolesti u pacientů s MD. Možnost neuropatické komponenty bolesti u pacientů s MD podporuje i vyhodnocení výsledků dotazníků PainDETECT a NPSI v naší studii. Dotazník PainDETECT, vytvořený cíleně za účelem identifikace neuropatické komponenty smíšených bolestí, prokázal při použití cut-off hodnot doporučených autory dotazníku neuropatickou komponentu bolesti jako možnou či pravděpodobnou u více než poloviny našeho souboru MD2 pacientů. Dotazník přitom dle recentních studií vykazuje u pacientů se smíšenou (např. radikulární) bolestí spíše nižší senzitivitu a řada autorů doporučuje snížení hodnoty cut-off. V nedávno publikované studii zaměřené na pacienty s radikulární bolestí vykazoval dotazník nejlepší diagnostickou validitu při cut-off hodnotě 11, ani pak však senzitivita nepřesáhla 70 % [25]. Velmi podobné závěry poskytuje jiná recentně publikovaná studie zaměřená na výskyt neuropatické komponenty bolesti u různých typů vertebrogenních onemocnění (vč. subakutní radikulopatie a lumbální stenózy) [26]. Uvedené závěry proto naznačují, že reálný výskyt neuropatické komponenty smíšených bolestí je pravděpodobně ještě vyšší, než prokazuje dotazník PainDETECT prostřednictvím původně doporučených cut-off hodnot. Při použití cut-off 11, doporučovaného v Eppingově studii, by v našem souboru pacientů byla neuropatická komponenta bolesti prokázána dokonce u 14 pacientů (60,1 %).

Velmi podobné výsledky naznačuje i druhý z použitých dotazníků, tedy NPSI, vytvořený primárně za účelem detailního popisu klinických symptomů neuropatické bolesti. Alespoň některé z deskriptorů, které jsou využívány v tomto dotazníku a poukazují na možný neuropatický charakter bolesti, jsme prokázali téměř u všech vyšetřovaných pacientů. Žádný z těchto deskriptorů však samozřejmě není pro neuropatickou bolest zcela specifický a může se vyskyto-

vat i u některých pacientů s bolestí nociceptivní. Většina pacientů nicméně vykazovala kombinaci více zmíněných deskriptorů bolesti a také výskyt doprovodných senzitivních symptomů charakteru mravenčení a/nebo brnění, což dále podporuje hypotézu možného podílu neuropatické komponenty bolesti u pacientů s MD2. Obecně je pro odlišení neuropatické a nociceptivní bolesti pomocí tohoto dotazníku nutné využít právě specifickou kombinaci zmíněných deskriptorů, kterou poskytuje např. pro tento účel vytvořené diskriminační skóre ($NPSI_{cz\text{-}D}$) [15]. S použitím tohoto skóre byl neuropatický charakter bolesti prokázán u 22 pacientů s MD2 (95,7 %). Periferní neuropatická bolest byla tímto způsobem konfirmována u 20 pacientů (87 %). Výskyt neuropatické komponenty bolestí by tak s použitím tohoto dotazníku byl dokonce ještě vyšší než u dotazníku PainDETECT. Tyto hodnoty je však nutné brát s určitou rezervou, protože se nejedná o originální zaměření dotazníku NPSI.

U 47,8 % pacientů byla dle dotazníku PainDETECT neuropatická komponenta bolesti hodnocena jako nepravděpodobná. U těchto pacientů je tedy zřejmě dominující podíl bolesti nociceptivní. Pravděpodobnou nociceptivní komponentu bolesti podporuje i časté užívání nesteroidních antirevmatik, které bylo v naší studii zjištěno v hodnoceném souboru pacientů s MD2 a bolestí, i když většinou pouze s částečným efektem. Bolest u pacientů s MD se tak jeví jako bolest smíšeného typu s variabilním podílem nociceptivní a neuropatické komponenty u různých pacientů.

Komplexní QST protokol je v rámci výzkumných projektů zaměřených na neuropatickou bolest standardně využíván pro potřeby objektivizace poruch senzitivní percepce v oblasti bolesti jako jednoho z významných pilířů nutných pro stanovení diagnózy neuropatické bolesti [18,27,28].

V naší studii jsme u vyšetřených pacientů s MD2 zachytili na DKK především změny v termických modalitách QST (hypestezii pro chlad a trend k hypestezii pro teplo a širšímu teplotnímu rozmezí, které pacient vnímá jako teplotně neutrální). Současně bylo přítomno paradoxní vnímání chladných podnětů jako tepla, tedy porucha diskriminace chladných podnětů, které pacient vnímá jako teplé či horké. Při vyhodnocení mechanických algických parametrů QST testovaných pomocí kalibrovaných špendlíků vykazovali pacienti s MD2 na HKK i DKK signifikantní pokles algického prahu (tedy hyperalgezii) pro ostrou mechanicky vyvolanou bolest. S popsanou hyperalgezii pro mechanické algické podněty je však v rozporu průkaz relativně snížené WUR, která byla zachycena na HKK u MD2 pacientů při srovnání se zdravými dobrovolníky. Tento rozdíl je však pravděpodobně podmíněn spíše náhodným výskytem vyššího počtu zdravých kontrol s abnormálně zvýšenou časovou sumací v této distribuci v našem kontrolním souboru. Pacienti kontrolního souboru pro tuto studii byli vybráni z větší skupiny zdravých kontrol, jejíž nálezy byly publikovány [18]. V každém souboru zdravých dobrovolníků se vyskytuje určitý počet jedinců s abnormálním nálezem testovaných parametrů (při nastavení norem pomocí 5. a 95. percentilu jde o 10 % hodnot kontrolního souboru). Výběr kontrol do tohoto užšího souboru byl proveden za účelem zajištění co nejlepší shody s demografickými charakteristikami (věk, pohlaví) souboru pacientů s MD2. Shodou okolností však byl při naplnění uvedených kritériích výběru do souboru zařazen vyšší počet kontrol (5) s abnormálně zvýšenou časovou sumací. Tento rozdíl proto nelze interpretovat jako průkaz snížené časové sumace u pacientů s MD2 (kde byly hodnoty tohoto parametru u všech pacientů v buď mezích normy, nebo dokonce s abnormálně zvýšenou časovou sumací).

Pouze jediná dosud publikovaná studie hodnotila kvantitativní testování senzitivity u pacientů s MD2 [29]. Srovnatelně s našimi výsledky kolektiv německých autorů popsal ve své studii pokles algického prahu pro ostrou mechanicky vyvolanou bolest u pacientů s MD2. Zajímavé zjištění v německé studii však bylo to, že pokles algického prahu byl přítomen u obou skupin pacientů s MD2 bez rozdílu, zda pacienti bolest popisovali či nikoliv, zatímco vnímání bolestivých podnětů (hypersenzitivita) a časová su-

Tab. 4. Kvantitativní testování senzitivity na horních končetinách: základní hodnoty.

QST parametr[1]	Pacienti s MD2 (n = 23)	Kontrolní skupina (n = 24)	p[2]
CDT	–1,6 (–2,8; –0,8)	–1,4 (–3,4; –0,9)	0,283
WDT	1,9 (1,1; 4,8)	1,8 (1,0; 3,2)	0,259
TSL	3,7 (1,9; 8,0)	3,2 (2,1; 6,2)	0,246
CPT	11,2 (2,9; 28,2)	13,5 (0,0; 26,5)	0,157
HPT	47,1 (39,0; 50,0)	45,5 (37,2; 50,0)	0,292
PPT	503,3 (284,7; 921,0)	573,3 (388,8; 859,4)	0,544
MPT	18,4 (5,8; 223,4)	40,8 (12,3; 121,2)	0,014
MPS	1,6 (0,2; 34,3)	3,2 (0,5; 6,1)	0,292
WUR	1,6 (1,0; 6,4)	3,8 (1,2; 6,9)	0,038
MDT	0,3 (0,2; 5,9)	0,4 (0,2; 1,4)	0,503
VDT	8,0 (7,7; 8,0)	8,0 (7,1; 8,0)	0,745
PHS	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)	0,328
DMA	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)	0,992

[1] Data jsou uvedena jako medián (5.–95. percentil).

[2] Srovnání hodnot jednotlivých QST parametrů mezi pacienty s MD2 a zdravými dobrovolníky bylo provedeno pomocí Mann-Whitneyova U testu.

CDT – senzitivní práh pro chlad (cold detection threshold); CPT – termoalgický práh pro chlad (cold pain threshold); DMA – dynamická mechanická alodynie (dynamic mechanic allodynia); HPT – termoalgický práh pro teplo (heat pain threshold); MD2 – myotonická dystrofie 2. typu; MDT – senzitivní práh pro mechanickou kožní citlivost (mechanical detection threshold); MPS – senzitivita pro ostrou, mechanicky vyvolanou bolest (mechanical pain sensitivity); MPT – algický práh pro ostrou, mechanicky vyvolanou bolest (mechanical pain threshold); PHS – paradoxní vnímání chladných podnětů jako horkých (paradoxial heat sensation); PPT – algický práh pro hlubokou tlakovou bolest (pressure pain threshold); QST – kvantitativní testování senzitivity (quantitative sensory testing); TSL – teplotní rozsah, vnímaný jako neutrální (thermal sensory limen); VDT – senzitivní práh pro vibrační čití (vibration detection threshold); WDT – senzitivní práh pro teplo (warm detection threshold); WUR – časová sumace ostrých mechanicky vyvolaných bolestivých podnětů (wind-up ratio)

Tab. 5. Kvantitativní testování senzitivity na dolních končetinách: základní hodnoty.

QST parametr[1]	Pacienti s MD2 (n = 23)	Kontrolní skupina (n = 24)	p[2]
CDT	–6,7 (–12,5; –1,4)	–4,0 (–8,6; –2,3)	0,064
WDT	11,3 (3,8; 15,9)	8,4 (3,7; 14,2)	0,307
TSL	19,2 (6,4; 25,4)	12,6 (6,0; 21,2)	0,085
CPT	17,8 (0,0; 26,1)	11,6 (0,0; 26,3)	0,406
HPT	48,3 (45,0; 50,0)	47,4 (41,2; 50,0)	0,717
PPT	540,0 (300,0; 964,0)	593,3 (409,5; 1133,7)	0,205
MPT	11,3 (5,7; 118,6)	48,5 (7,2; 126,7)	0,051
MPS	1,3 (0,4; 25,4)	2,6 (0,4; 18,2)	0,413
WUR	2,7 (1,2; 5,9)	2,5 (1,3; 7,4)	0,602
MDT	0,8 (0,3; 6,6)	0,9 (0,4; 6,4)	0,67
VDT	8,0 (5,3; 8,0)	8,0 (7,0; 8,0)	0,551
PHS	0,0 (0,0; 3,0)	0,0 (0,0; 1,0)	0,03
DMA	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)	0,349

[1] Data jsou uvedena jako medián (5.–95. percentil).

[2] Srovnání hodnot jednotlivých QST parametrů mezi pacienty s MD2 a zdravými dobrovolníky bylo provedeno pomocí Mann-Whitneyova U testu.

CDT – senzitivní práh pro chlad (cold detection threshold); CPT – termoalgický práh pro chlad (cold pain threshold); DMA – dynamická mechanická alodynie (dynamic mechanic allodynia); HPT – termoalgický práh pro teplo (heat pain threshold); MD2 – myotonická dystrofie 2. typu; MDT – senzitivní práh pro mechanickou kožní citlivost (mechanical detection threshold); MPS – senzitivita pro ostrou, mechanicky vyvolanou bolest (mechanical pain sensitivity); MPT – algický práh pro ostrou, mechanicky vyvolanou bolest (mechanical pain threshold); PHS – paradoxní vnímání chladných podnětů jako horkých (paradoxial heat sensation); PPT – algický práh pro hlubokou tlakovou bolest (pressure pain threshold); QST – kvantitativní testování senzitivity (quantitative sensory testing); TSL – teplotní rozsah, vnímaný jako neutrální (thermal sensory limen); VDT – senzitivní práh pro vibrační čití (vibration detection threshold); WDT – senzitivní práh pro teplo (warm detection threshold); WUR – časová sumace ostrých mechanicky vyvolaných bolestivých podnětů (wind-up ratio)

Tab. 6. Nálezy sebehodnotících psychologických dotazníků a jejich srovnání mezi kontrolní skupinou a pacienty s MD2.

Dotazník[1]	Pacienti s MD2 (n = 23)	Kontrolní skupina (n = 24)	p[2]
BDI	17,7 (10,3)	5,9 (4,4)	<0,001
PCS	18,9 (12,3)	0,0 (0,0)	<0,001

[1] Data jsou prezentována jako průměr (směrodatná odchylka).

[2] Srovnání jednotlivých dotazníků mezi pacienty s MD2 a zdravými kontrolami, provedené pomocí nepárového t-testu.

BDI – Beck Depression Inventory; MD2 – myotonická dystrofie 2. typu; PCS – Pain Catastrophizing Scale

mace bolesti byly zvýšeny pouze ve skupině pacientů s přítomností bolesti. V naší studii jsme vyšetřovali pouze pacienty s bolestí, a k případným změnám senzitivní percepce u pacientů bez bolesti se tedy nemůžeme vyjádřit. Hypersenzitivita pro mechanické algické podněty popisovaná autory citované studie nebyla v našem souboru na skupinové úrovni prokázána. Na individuální úrovni však byla přítomna u řady našich pacientů (5/23 pacientů na HKK, 4/23 pacientů na DKK), což lze v souladu se snížením algických prahů očekávat. Nejvýznamnější prokázanou abnormitou QST v uvedené německé studii [29] bylo snížení algického prahu pro PPT. V naší skupině vyšetřených pacientů s MD2 jsme významné změny tohoto parametru překvapivě nezaznamenali. Pravděpodobným vysvětlením je významně vyšší počet svalů, na nichž byl v německé studii [29] PPT testován (a to vč. řady svalů proximálních). V naší studii byl tento parametr vyšetřen pouze v rozsahu obvykle testovaném v rámci DFNS/QST protokolu. Nálezy tohoto parametru nejsou tedy vzhledem k rozdílnému rozsahu vyšetření mezi oběma studiemi srovnatelné.

Naše výsledky naopak prokázaly zřetelný trend k výskytu abnormit termického čití, který nebyl zachycen autory publikované německé práce [29]. Tyto změny v našem souboru by mohly poukazovat na možnou dysfunkci tenkých nervových vláken, a jsou tedy v korelaci s charakterem bolesti prokazovaným pomocí dotazníkových nástrojů. Senzitivní profil pacientů s bolestí při MD2 je velmi podobný profilu, který je prokazován u pacientů s fibromyalgií. Podobně jako pacienti v našem MD2 souboru vykazují i jedinci s fibromyalgií generalizovanou přecitlivělost na mechanické algické podněty, zatímco modality doteku jsou obvykle neovlivněny [30]. Bolest u fibromyalgie je podle recentních studií alespoň u části pacientů podmíněna postižením tenkých nervových vláken [8,23,31], přičemž dysfunkce tenkých nervových vláken se u těchto pacientů manifestuje právě hypestezií pro termické podněty [31]. Bolest při fibromyalgii a MD má přitom řadu podobných rysů a často obdobný charakter. Průkazem této skutečnosti je studie, v níž byla v náhodně vyšetřeném souboru šedesát tří pacientů, kteří byli sledováni pro fibromyalgii, u dvou pacientů geneticky verifikována MD2 [32].

V souhrnu tedy QST nálezy podporují koncept možné poruchy funkce tenkých vláken u pacientů s MD, což svědčí pro přítomnost neuropatické komponenty bolesti u této diagnostické jednotky.

Vyhodnocením sebehodnotících psychologických dotazníků jsme u pacientů s bolestí při MD2 prokázali významně vyšší výskyt depresivních symptomů a vyšší míru katastrofizace bolesti. Zjištěné výsledky však neumožňují rozlišit, zda se zmíněné psychologické charakteristiky vztahují k základnímu onemocnění (MD2) nebo jsou asociovány s bolestí. U MD bývá obvykle popisováno zvýšené riziko deprese (podobně jako u jiných chronických onemocnění), a to zejména vzhledem k progresivnímu charakteru

tohoto onemocnění a jeho omezené terapeutické ovlivnitelnosti [33,34]. Kromě asociace se základním onemocněním byl však popsán i zvýšený výskyt depresivní symptomatiky u pacientů s bolestí při MD2 [8]. V případě, že se změny psychologických charakteristik vztahují k bolesti, také není jasné, zda jsou tyto změny důsledkem bolestivého stavu nebo jeho příčinou (což opět nelze ze stávajících dat validně odlišit). Obě situace jsou podle dosud publikovaných studií možné a poměrně časté: metaanalýza 56 studií zaměřená na vzájemný vztah bolesti a deprese u různých onemocnění prokázala průměrný výskyt bolesti u depresivních stavů přibližně v 65 %. Naopak výskyt deprese u pacientů s bolestí se u různých klinických jednotek pohyboval v širokém rozmezí mezi 13 a 85 % [35]. Pro zpřesnění interpretace změn popsaných psychologických charakteristik v rozvoji bolesti při MD2 by proto bylo třeba vyšetřit pomocí identických dotazníků pacienty s MD2, kteří bolesti nemají, a optimálně také dlouhodobě sledovat pacienty s bolestí při MD2 a vyšetřit je pomocí používaných dotazníků opakovaně v různých stadiích onemocnění (což umožní ozřejmit, zda jsou zvýšená míra deprese a další specifické psychologické charakteristiky u pacientů patrné již před rozvojem bolesti nebo se objevují až v jejím důsledku).

Omezení studie

Určitým omezením prezentované studie je malý rozsah hodnocené skupiny pacientů a absence „kontrolní" skupiny pacientů s MD2 bez bolesti. Omezený rozsah testované skupiny je podmíněn skutečností, že jde o vzácné onemocnění, navíc často asociované s řadou komorbidit vč. endokrinních onemocnění (např. diabetes mellitus), které představovaly vylučující kritérium pro vstup do této studie (aby nebyly výsledky zkresleny případnými jinými typy bolesti – např. při diabetické polyneuropatii). Navýšení počtu pacientů v testované skupině je tedy obtížně realizovatelné. Větší rozsah testovaného vzorku pacientů by přitom pravděpodobně zvýšil statistickou významnost zachycených rozdílů a zlepšil by tak validitu výstupů. Doplnění kontrolní skupiny bude realizováno v rámci navazujícího projektu, který v současnosti probíhá na pracovišti autorů. Výsledky této pilotní studie by bylo vhodné ověřit rovněž prostřednictvím objektivních metod konfirmujících postižení silných a tenkých nervových vláken (tedy EMG vyšetření a kožní biopsie či korneální konfokální mikroskopie a/nebo specifických modalit evokovaných potenciálů zaměřených na hodnocení funkce tenkých nervových vláken a/nebo navazujících nociceptivních drah). Doplnění popisovaných modalit bude též provedeno v popisované navazující studii.

Určitým limitem zjištěných nálezů je také validace použitých dotazníků. Jediným v českém jazyce validovaným dotazníkem pro diagnostiku neuropatické bolesti je dotazník NPSI (Šrotová et al 2015). Tento dotazník je však primárně zaměřen pouze na detailní popis neuropatické bolesti, a nikoli na její diskriminaci oproti bolesti nociceptivní. K tomuto účelu byl proto v provedené studii využit dotazník PainDETECT. Tento dotazník je v českých podmínkách rutinně využíván v klinické praxi, a to navzdory skutečnosti, že jeho česká verze nebyla validována. Validační studie tohoto dotazníku nyní probíhá na pracovišti autorů. V jejím úvodu byla ověřena využitelnost komerčně distribuované verze dotazníku metodou zpětného překladu („forward-backward translation") a nebyl shledán rozpor s verzí originální. Dotazník je tedy využitelný v komerčně distribuované verzi, jeho validací se nyní intenzivně zabýváme. Obdobně dotazník Pain Catastrophizing Scale se ve výzkumné praxi používá dlouhodobě. Česká verze dotazníku je dostupná na oficiálních stránkách tvůrců testu. Překlad proběhl formou „forward-backward translation", avšak dotazník neprošel žádnou oficiální validační studií.

V neposlední řadě může určitý limit představovat i cílené zaměření použitých diagnostických nástrojů na neuropatickou bolest a menší pozornost věnovaná nociceptivní komponentě bolestí. Pro tento účel by zřejmě bylo v navazujících studiích vhodné využít k detailní fenotypizaci pacientů také dotazníky, které lépe reflektují nociceptivní komponentu bolesti.

Závěr

Deskriptory bolesti u pacientů s MD2 v použitých dotaznících, a částečně i senzitivní profil těchto pacientů stanovený pomocí QST podporují hypotézu, že bolest u MD2 má také neuropatickou komponentu. Pacienti s bolestí při MD2 vykazují vyšší míru depresivní symptomatiky a katastrofizace bolesti. Provedená studie však neumožňuje rozlišit, zda se změny těchto psychologických charakteristik vztahují k bolesti či k základní diagnóze jako takové.

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16. Summary

Myotonic dystrophy 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 several organ systems. Clinically, this multisystemic disorder is characterized by muscular and high variability of extramuscular symptoms. The typical MD1 phenotype is characterized by a distinctive combination of muscular symptoms, such as facial weakness with ptosis, grip myotonia, and distal muscle weakness with muscular atrophy. Clinical symptoms of MD2 patients have large phenotypic variability from asymptomatic patients to severe muscular weakness. Myotonic dystrophy presents with a high variability of symptoms and multi-organ involvements, involving the cardiovascular, endocrine, central nervous, respiratory, gastrointestinal, ophthalmologic, or genitourinary systems. We identified frequently observed symptoms in patients with myotonic dystrophy that were less reported in the literature. Based on the information obtained we focused mainly on identifying the fertility impairment in myotonic dystrophy, the character of pain, and myotonia assessment.

Reproductive abnormalities are a well-recognized finding in myotonic dystrophy because of the involvement of reproductive and endocrine systems. In MD1 women, fertility impairment is considered highly probable. But only limited and inconsistent data existed concerning the fertility of women patients with myotonic dystrophy type 2. A decreased ovarian reserve is one of the factors assumed to be involved in fertility impairment. AMH is considered the best measure of ovarian reserve. In our study, we confirmed that MD1 females show a significant decrease of AMH values, moreover our study extends these results to the general MD1 population (ie, not only those women with clinically clear fertility impairment reported previously in the literature). AMH levels were similar between females with MD2 and controls. Therefore we suggest decreased ovarian reserve in women with MD1, but not in MD2.

Pain is often a symptom for patients with myotonic dystrophy. It may fluctuate over time and can be influenced by exercise, palpation, and cold temperature. Patients complain of various types of pain, myalgia, and cramps, most often located in the thighs, back, and proximal upper limbs. The etiology of pain in MD is unknown and is probably to be multifactorial. An abnormal load on the musculoskeletal system due to muscle imbalance of weak muscle groups, or due to deep muscle myotonia, could be one of the causes of pain. Nevertheless, some of the pain descriptors indicate the possibility of the neuropathic component of pain in MD patients. We found that the frequency of long-term muscle pain seems to be similar in

both types of myotonic dystrophy and its frequency is about 55%. Also, the pain intensity seems to be identical in both MD types. The PainDETECT questionnaire showed the presence of a neuropathic component of pain in more than half of the MD2 patients examined in our study. QST (Quantitative Sensory Testing) has shown frequent occurrences of thermal and algic sensory abnormalities. Altogether we found no significant differences in the frequency, quality, and severity of pain between the different types of the disease. The pain descriptors and sensitivity profile support the hypothesis that pain in MD2 is also likely to have a neuropathic component.

Myotonia is defined as delayed relaxation of skeletal muscle after voluntary muscle contraction or external mechanical stimulation (e.g. percussion) and thus reflects a state of muscle fiber hyperexcitability. Pathophysiological, myotonia is caused by permanent depolarization of sarcolemma due to impaired chloride or sodium ion channels of the muscle membrane. In MD1 patients myotonia is a frequent symptom, nearly as muscle weakness. In MD2 patients myotonia is often less apparent compared with patients with MD1 and is usually mild to moderate intensity. The clinical evidence of myotonia (grip or percussion) is observed on neurological examination only in a minority of MD2 patients. Nevertheless, we can find a large range of reported occurrences of myotonia in MD2 patients. This could be due to inconsistencies in the assessment of myotonia between a history of myotonia reported by patients and the clinical evidence of the myotonic phenomenon. Even severe myotonia could be observed in some MD2 patients. In our study, we focused on myotonia assessment by a commercially available dynamometer. All MD1 patients and half of the MD2 patients exceeded the upper limit of normal relaxation time after voluntary contraction (which indicates the myotonia) using a dynamometer. Therefore a commercially available dynamometer provides a valid and reliable quantitative measure of grip myotonia suitable as part of routine examinations to gather data on the natural history of myotonic disorders.

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