Core Clinical Phenotypes in Myotonic Dystrophies

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Myotonic dystrophy type 1 (DM1) and type 2 (DM2) represent the most frequent multisystemic muscular dystrophies in adulthood. They are progressive, autosomal dominant diseases caused by an abnormal expansion of an unstable nucleotide repeat located in the non-coding region of their respective genes DMPK for DM1 and CNBP in DM2. Clinically, these multisystemic disorders are characterized by a high variability of muscular and extramuscular symptoms, often causing a delay in diagnosis. For both subtypes, many symptoms overlap, but some differences allow their clinical distinction. This article highlights the clinical core features of myotonic dystrophies, thus facilitating their early recognition and diagnosis. Particular attention will be given to signs and symptoms of muscular involvement, to issues related to respiratory impairment, and to the multiorgan involvement. This article is part of a Special Issue entitled “Beyond Borders: Myotonic Dystrophies—A European Perception.”

Keywords: myotonic dystrophies, DM1, DM2, phenotypes, myotonia, sleep disorders, repeat expansion diseases

INTRODUCTION

The genetic background of myotonic dystrophies type 1 and 2 (DM1 and DM2) is due to repeat expansions of unstable nucleotides in untranslated DNA regions causing mis-splicing of mRNAs, which affects almost all cells and organs of the human body. This sum of alterations leads to an extremely heterogeneous phenotype with multisystemic involvement. Many findings and symptoms of DM1 and DM2 overlap, but important differences usually allow their prompt clinical distinction (Table 2). Both types of myotonic dystrophies represent the most common inherited muscle disorders in adulthood with regional variations in prevalence and incidence. In general, DM1 occurs more frequently than DM2, with some exceptions in northern and mid European countries such as Finland, Germany, and Czech Republic, where DM1 and DM2 are almost equally represented. Table 1 provides a useful summary of the country-specific prevalences (1–4).

KEY ASPECTS IN MYOTONIC DYSTROPHY TYPE 1

For DM1, there is a rough correlation between the expansion of CTG-repeats and the onset of symptoms as well as the severity of the disease; nevertheless predictions about the clinical features and the progression of the disease based on CTG-repeat size should be made very carefully (23, 24). 5 to 37 CTG-repeats are physiologic in healthy individuals. An expansion between 38 and 49 repeats does not show a linear and strict relationship and thus may overlap (25, 26):

- a mild phenotype with an expansion of 50–150 CTG-repeats,
- a classic phenotype with a wide span from mild to severe symptoms and an expansion of 50–1,000 CTG-repeats,
- a childhood/juvenile phenotype with early-onset and typically >800 CTG-repeats, and
- the most severe "congenital form" with usually >1,000 CTG-repeats.
CTG-repeats will expand in every following generation, and fully penetrant alleles occur with >50 CTG-repeats. This results in the so-called anticipation, a clinical term describing an earlier onset with a more severe phenotype in the next generations (26). Furthermore, the repeat instability leads notably to premature aging of almost all organs, so DM1 may be counted among the progeroid diseases (27). The most typical appearance of DM1 is the “adult-onset” or “classic” phenotype with a CTG-repeat size ranging from 50 to <1,000. It is characterized by a distinctive combination of muscular symptoms, such as facial weakness, ptosis, grip myotonia, and distal muscle weakness with muscular atrophy. The classic phenotype is typically accompanied by extramuscular symptoms like cognitive impairment, cataracts, and diabetes mellitus. Nevertheless, as this multisystem disorder often presents with a high variability, some patients may primarily show only non-specific extramuscular symptoms like fatigue, daytime sleepiness, gastrointestinal symptoms, or cardiac conduction defects in an early stage of the disease, which could delay the diagnosis. Mildly affected patients with CTG-repeat sizes 50–100 may have normal or only minimally shortened lifespan (28). Because of comorbidities, such as cardiac and pulmonary complications, life expectancy is, however, reduced in about 70% of the patients with the classic phenotype (25).

### SPECIAL ASPECTS IN MYOTONIC DYSTROPHY TYPE 2

DM2 (also referred to as proximal myotonic myopathy) is caused by the expansion of the tetranucleotide CCTG-repeat in the first intron of CNBP (cellular nucleic acid-binding protein), formerly known as zinc finger protein 9 (ZNF9) gene (29). Similar to DM1, these expansions are extremely unstable, causing widespread cellular abnormalities of mRNA splicing. In DM2, the expansion ranges from 75 to 11,000 with a mean of 5,000 CCTG-repeats. In contrast to DM1, there is no correlation between clinical phenotype and CCTG-repeat length and no anticipation has been observed (29, 30).

### MUSCULAR SYMPTOMS

#### Muscular Weakness

The symptoms myotonia, muscular weakness, and muscular atrophy are the principal traits of DMs and gave the eponym for these two types of the disease. In DM1, patients present with characteristic distally predominant muscular atrophy and weakness mainly involving finger flexors, wrist flexors, and foot extensors (Figures 1A–B). The latter will cause foot drop and gait disturbance with repeated falls and injuries (31). In contrast to this, muscle weakness in DM2 is typically proximal and axial, affecting more consistently the neck flexors, hip flexors, and hip extensors (Figure 1C) (30, 32). 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 (33, 34). Muscle weakness is one of the most frequently reported symptoms in DM1 (>45% of patients with adult phenotype) and

| TABLE 1 | Country-specific prevalences of DM1 and DM2. |
|--------------------------|-----------------|-----------------|-----------------|
| Country                  | Disease         | Prevalence (x10^6) | Reference |
| Croatia                  | DMs             | 18.1             | (5)          |
| Czech Republic           | DM2             | DM2 > DM1        | (6)          |
| Finland                  | DM2             | 10               | (7)          |
| Finland                  | DM2             | 54               | (8)          |
| Germany                  | DM2             | DM1 = DM2        | (9)          |
| Israel                   | DM1             | 15.7             | (10)         |
| Italy                    | DMs             | 2.1              | (11)         |
| Italy                    | DM1             | 9.3              | (12)         |
| Italy                    | DM2             | 0.9–1.1          | (13)         |
| Italy                    | DM1             | 9.6–11.7         | (13)         |
| Japan                    | DMs             | 9.1              | (14)         |
| Spain, Mallorca          | DMs             | 10.8             | (15)         |
| New Zealand, Otago       | DMs             | 11.6             | (16)         |
| North Ireland            | DMs             | 11.9             | (17)         |
| North Ireland            | DMs             | 34               | (18)         |
| North UK                 | DM1             | 10.4             | (19)         |
| Quebec                   | DM1             | 210              | (20)         |
| Serbia, Belgrade         | DM1             | 5.3              | (21)         |
| Taiwan                   | DM1             | 0.5              | (22)         |

| TABLE 2 | Core Clinical Symptoms helpful for differentiating DM1 and DM2. |
|--------------------------|-----------------|-----------------|-----------------|
| DM1                      | DM2             |
| Age of onset             | Depends on CTG-repeat-size, in common first symptoms earlier than in DM2 | 30–40         |
| Family history           | Increasing severity of symptoms throughout generations (anticipation) | Variability in symptoms, but no evidence for anticipation |
| General appearance       | Forehead balding | Myopathic face, temporal wasting, ptosis |
|                          | Myopathic face, temporal wasting, ptosis | Frequent: nasal/slurred speech, dysphagia |
|                          | Distal | In some cases: dysphagia |
| Muscle                   | Distal | Proximal and axial |
|                          | Myotonia | mild proximal |
|                          | Myopathy | Proximal, late |
|                          | Atrophy | Predominant |
|                          | Myalgia | |
| Sleep disturbances       | Central sleep apnea, obstructive sleep apnea, respiratory muscle weakness | Central sleep apnea |
| Central nervous system   | In almost every patient | Frequent |
|                          | Rare in adults, more frequent in congenital DM | In some patients |
|                          | | Frequent |
| Diagnostics              | Electromyography | Myotonic discharges in clinically affected and not affected muscles |
|                          | | Proximal, but can be absent |
DM2 (40–55% of patients) (26, 32). Figure 1D illustrates the predominantly affected muscle groups of patients with DM1 and DM2 (see Table 2 for differentiating DM1 and DM2).

The typical facial appearance of DM1 patients (“myopathic face”—“hatchet face”) is a prominent and early feature and is caused by weakness and atrophy of facial muscles and ptosis that might give the false impression of a tired, sad, or emotionless patient (35). Balding of the forehead and atrophying of the temporal muscle are often seen (Figure 2) and completes the overall picture of a patient with DM1. Severe weakness of orbicularis oculi muscles cause not only ptosis but also insufficient eyelid closure with risk of recurrent conjunctivitis. This facial muscle involvement is usually not seen in DM2 patients, thus it may help in differentiating DM1 from DM2 patients (Table 2).

Especially in patients with DM1, the speech can be nasal and slurred, due to the weakness of oropharyngeal muscles, sometimes causing chewing and swallowing difficulties.

Myotonia

Myotonia is a more frequent symptom in DM1 mainly affecting the fingers (grip myotonia), the jaw, and the tongue (36). Clinically, a warm-up phenomenon is usually observed when myotonia improves with repeated contractions, which is mostly true for grip myotonia, but also for myotonia of the tongue and the jaw (37, 38). An increased excitability of muscle fibers is thought to be the cause for myotonia, leading to continuous discharges of repetitive action potentials after voluntary contraction or mechanical stimulation (39) in electromyography (EMG). These myotonic runs can be detected with EMG even in clinically unaffected muscles of DM1 patients, but can be rare or even be absent in DM2 (40). On a molecular basis, it has been suggested that myotonia is caused by mis-splicing of the chloride channel (CLCN1, ClC-1) due to misregulated MBNL1 and CUGBP1
Recent studies have investigated the relationship between a central nervous system involvement and myotonia, suggesting that myotonia should no longer be considered as a solitary peripherally triggered muscular symptom (42, 43). In one fMRI study, higher cerebral blood oxygen level-dependent signals (BOLD) in specific primary and secondary motor areas were found during myotonia episodes. This was interpreted as a relationship between myotonia and high-order motor control areas (44). In another study, the severity of myotonia correlated with diffuse white matter alterations in specific primary and secondary motor areas (45). There are contradictory reports about the correlation between myotonia, grip strength, and CTG-repeat length (46, 47) for DM1 patients. Overall, grip strength correlates negatively with CTG-repeat length in most studies, but this is not necessarily true for myotonia. In one recent study, there was a statistically significant correlation between grip myotonia and CTG-repeat length, but this was not clinically meaningful and not predictive (47).

Myotonia seems to be usually mild to moderate or even absent in many DM2 patients, impacting only minimally their quality of life (36). However, its occurrence in different cohorts ranges between 24 and 75% (30, 32, 40). This variability is partly due to the discrepancy sometimes observed between history of myotonia reported by patients and the clinical evidence of myotonic phenomenon, which is observed on neurological examination only in a minority of DM2 patients. Few patients may, however, display a severe myotonia and in some of these cases additional mutations in ion channel genes CLCN1 and SCN4A have been identified (48, 49). It is, therefore, advisable to screen atypical cases with severe myotonia for mutation in these genes that act as phenotype modifier enhancing the myotonic phenomenon in DM2 (49). Particularly limb girdle myotonia is frequently neglected and underdiagnosed. With aging, the presence of myotonia gradually becomes less clinically relevant as it is overwhelmed by the gradually worsening of muscle weakness (32). This trend is also confirmed in studies assessing quality of life of DM2 patients, where significant predictors of worse QoL (quality of life) were older age, worse muscle strength, and higher level of fatigue (50).

Musculoskeletal Pain or Myalgia

Musculoskeletal pain or myalgia may be present in some DM1 patients, but is less frequent in comparison to DM2 (Table 2). However, with the progression of the disease, a muscular imbalance due to weakness may occur and secondary complications such as regional myofascial pain or joint pain syndromes may develop even in DM1. In DM2, about 60% of patients complain of diffuse myalgia. These are usually exercise-related and worsen in cold temperatures (33, 51). Some patients consider pain as the most disabling symptom of the disease also because of its poor response to common analgesics (7). The pathophysiological mechanism of myalgia in DM2 is yet to be elucidated, but it is probably related to specific molecular changes occurring in the muscles of DM2 patients (52).

For adult-onset DM1, the first muscular symptoms can become apparent in early adulthood, but some patients may exhibit subtle symptoms like grip myotonia, ptosis or slurred speech in childhood. Patients with classic DM1 are typically diagnosed at around 30 years, but mildly affected patients with CTG-length 50–100 may present solely some slight myotonia or cataracts and may have their diagnosis delayed until they are around 40 years old (28). The clinical onset of DM2 typically occurs later than DM1, around the third to fourth decade; it may, however, often go unrecognized for several years due to only mild or unspecific clinical symptoms like myalgia or muscle cramps.

Muscular Respiratory Symptoms

Respiratory muscle weakness will occur in a high percentage of the patients with DM1 in an early stage of the disease and chronic respiratory failure may develop (53). Expiratory muscles seem to be affected sooner than inspiratory muscles, resulting in early recurrent pneumonia due to a weak cough and insufficient airway clearance. The exact prevalence of respiratory insufficiency in DM1 is unclear because symptoms of nocturnal hypoventilation overlap with typical neuropsychological symptoms like fatigue, daytime sleepiness, and concentration difficulties (54). As both respiratory muscle weakness and cardiac symptoms account most for the reduced survival of the patients, repeated testing for early diagnosis is essential. A pure respiratory muscle weakness rarely occurs in DM2 and only about 6–15% of patients require non-invasive ventilation (55).

EXTRAMUSCULAR SYMPTOMS

CNS Symptoms

Fatigue, daytime sleepiness, and concentration difficulties are frequently reported symptoms in DMs. In DM1, cognitive deficits were initially attributed to a low IQ or mental retardation, but recent studies show that this assumption was wrong for a large cohort of patients and mainly applies for cases of congenital myotonic dystrophy (CDM). In fact, for the classic phenotype of DM1, neuropsychological deficits are as variable as muscular symptoms, and even recent publications about the correlation of CTG-repeat size and neuropsychological deficits show contradictory study results (56–58). There seems to be a correlation between diffuse brain alterations in primarily white and secondary gray matter, linking the DM1 to the group of brain disconnection disorders (59). Caso et al. investigated 51 DM1 patients and found a correlation between changes in brain white matter and cognitive impairment (60). Cerebral white matter hyperintensities have been observed in both DM1 and DM2 patients, especially in those older than 40 years, but their clinical and functional significance still remains unclear (61–63). In a recent study about the educational profile of a large cohort of young DM1 patients, no significant differences compared to the healthy population were found (35), assuming that cognitive and concentration disturbances may occur later in the course of the disease in the context of a variable premature cognitive decline, as suggested by the study of Modoni et al. (56). Mild cognitive and behavioral symptoms are also present in DM2 patients. In particular, altered visuo-spatial and executive functions, reduced attention and flexibility of thinking, avoid-ant behavioral trait, and depression have been detected in these patients (63, 64). In many cases, neuropsychological disturbances
jeopardize the ability to work and reduce the quality of life more than muscular symptoms.

Excessive daytime sleepiness, fatigue, and concentration difficulties may also be caused by central sleep disturbances or sleep apnea. Sleep-disordered breathing is one of the earliest manifestations and occurs in a high percentage of patients with DM1 (65), but overlapping symptoms of nocturnal hypoventilation and CNS symptoms may delay diagnosis and treatment. Chronic central sleep-disordered breathing has an impact on quality of life, morbidity, and mortality and should be assessed frequently in every patient with DM1 (54, 55, 66).

Until now, little is known about changes in CNS causing cognitive deficits and central sleep disrupted breathing. Almost every clinical study is conducted with the usually more affected DM1 patients, therefore data for DM2 patients are limited. On a molecular basis, MBNL1 and probably CELF may both be involved in CNS alterations, but little is known about molecular defects causing highly variable CNS symptoms in DM1 (42, 43). The above mentioned aspects lead to a discussion as to whether CNS dysfunction is caused by altered neurodevelopment, by neuro-dysfunction or by neurodegeneration within the definition of progeroid diseases (67). The hypothesis of a neurodegenerative disease is endorsed by findings of tau pathology and neurofibrillary degenerations, even if no correlations with CTG-repeat length were found (68). Overall, CNS dysfunction seems to be multifactorial.

**Eyes**

The most frequent, early and typical extramuskular manifestation is the occurrence of early-onset cataract, observed in about 50–60% of patients (30, 32, 69). A medical history of cataract surgery in combination with muscular symptoms often leads to the diagnosis of DM, even in mildly affected patients without any sign of muscular impairment (70–72). The mechanisms underlying the pathophysiology of cataract in DMs are still largely unknown. At first, a potential effect of the CTG-mutation on the expression of neighboring genes such as SIX5 was considered in DM1 (73). But recent findings showed that SIX5 knock-out mice develop the nuclear type of cataract and not the posterior subcapsular/cortical type that are commonly observed in DMs. In addition, SIX5 is not adjacent to the DM2 repeat expansion so that this mechanism could not explain cataracts in DM2. More recent studies of global transcription performed on samples of lens epithelium in patients affected by DM1, DM2, and controls, identified a high similarity as regards the pattern of gene expression between DM1 and DM2 and hypothesized that common molecular mechanisms should be involved in cataract formation probably involving interferon signaling pathways (74, 75).

**Endocrine Symptoms**

Endocrine dysfunctions such as diabetes, hypogonadism, and secondary hyperparathyroidism with decreased Vitamin-D levels are frequent in DMs and their occurrence increases with progression of the disease (76–78). A cross-sectional study on 68 DM1 patients showed at least one endocrine dysfunction in 44% at baseline and in 84% after 8 years (76). Diabetes mellitus, if not properly treated, may complicate and aggravate the clinical picture due to diabetic polyneuropathy with worsening of gait instability and distal weakness. Hyperparathyroidism may contribute to fatigue and muscle impairment (76). More rarely, abnormalities in growth hormone secretion and glucose intolerance may be observed (79).

**Hearing Impairment**

Some degree of hearing loss has been described in DM2 since its first description (80). A recent systematic study on 56 Dutch and French DM2 patients then demonstrated that a mild to moderate hearing impairment was present in about 60% of examined patients. It is mostly a cochlear sensorineural hearing impairment which may be interpreted as an early presbycusis (81), well fitting in the interpretation of DMs as premature aging diseases. Similar features of cochlear impairment have also been described in some studies on DM1 patients (82).

**Cardiac Symptoms**

In DMs, cardiac involvement is common. Cardiologic comorbidities include arrhythmias, atrial fibrillation, and conduction defects (e.g., AV-blocks) and often requires the implantation of pacemakers. Other infrequent manifestations are sudden death, heart failure, Brugada syndrome, ischemic heart disease, and mitral valve prolapse (83, 84). Dilated cardiomyopathies may also occur in some patients, but are not frequently found. Cardiac abnormalities in DM2 are similar to those observed in DM1 but occur less frequently. According to a recent observational case–control study on a large cohort of DM2/DM1 patients, it emerged that electrocardiographic abnormalities as PR > 200 ms and QRS > 100 ms were more frequent in DM1 (respectively, 31 and 48%) than DM2 patients (10 and 17%). Of those, 6 DM2 vs. 28 DM1 patients needed a pacemaker/implanted cardioverter (85). In the same study, echocardiography did not show any significant structural abnormalities but it was previously reported that a cardiomyopathy might occur in about 3% of DM2 patients. In DM1, the severity of cardiac involvement seems directly related with the size of CTG-expansion as recently studied by Chong-Nguyen et al. (9, 30, 85, 86). Atrial fibrillations and arrhythmias increase the risk of cerebral ischemia (87) and mortality and morbidity significantly depend on early cardiologic diagnosis and treatment (83).

**Gastrointestinal Symptoms**

Along with elevations of creatine kinase, elevations of AST and ALT are frequent in patients with DM (88). In some cases, liver biopsies are performed because of these elevated “hepatic” enzymes without retrieving any pathologic result. The elevation of gamma-GT is suggested to be caused by contractions of bile canaliculi and bile ductules, whereas elevated levels of AST and ALT have their origin in skeletal muscle and go along with elevations of creatine kinase (89). Alternating constipation, pseudo-constipation, bloating, and diarrhea are frequently reported symptoms in DM1, accompanied by stomach cramps, reflux, and regurgitation. They are caused by involvement of smooth and striated muscles and endocrine dysfunctions (90, 91). Swallowing problems are typical for DM1 patients and due to reduced oral transport that is caused by myotonia and weakness of the tongue. Dysphagia is caused by
reduced swallowing reflex and reduced esophageal motility (92)
which causes the major clinical problem by risk of aspiration. In
conjunction with weakness of early affected expiratory muscles,
this results in recurrent pneumonia and increased risk of death.
A reduced or absent gastrointestinal peristaltic movement was
earlier shown in radiological studies as well as delayed intestinal
transits (93). Megacolon with the risk of ileus, volvulus and rup-
ture, is a significant and life-threatening complication. Delayed
emptying of the gall bladder may increase the risk for gallstones.

Cancer
A higher incidence for neoplasms was found in several studies
(28, 94, 95), most of them showed a predisposition in patients
with DM1 for cancers such as skin cancer (like benign calcify-
ing cutaneous tumors, pilomatricomas), thyroid, testicular, and
prostate cancer. Because of the limited number of high-quality
surveys and studies about the prevalence of cancer in DM1,
no epidemiologic correlation with a non-DM-population.

Peripheral Polyneuropathy
There is some debate as to whether peripheral neuropathy is a
multisystemic manifestation of DMs or are caused by metabolic
and endocrine dysfunctions. Its manifestation is not typical at
early stages of the disease but may occur in about one-third of
patients in later stages (97) of DM1 patients and contributes to
balance impairment and increased risk of falls (31, 98). There
were no significant correlations between age, duration of neu-
romuscular symptoms or CTG-repeat size (98, 99), suggesting that
the affection of peripheral nerve system is secondary to metabolic
and endocrine dysfunctions.

CONGENITAL MYOTONIC DYSTROPHY
(CDM)
Patients with congenital DM1 have large CTG-expansions of
more than 800, usually around 1,000. Characteristically, these
large expansions are caused by maternal transmission, but
CDM with paternal transmission is also known (23, 100–102).
Clinically, CDM patients are severely affected and symptoms are
often present before birth as polyhydramnios and reduced fetal
movement. Hypotonia, generalized weakness, hyporeflexia, bilat-
eral talipes, contractures, arthrogyrosis, facial dysmorphism (carp
mouth, ptosis, long neck and face, temporal muscle atrophy),
and a weak cry are typical symptoms at birth or in the first days
after delivery. Weak sucking and respiratory insufficiency often
make ventilatory support unavoidable. Respiratory insufficiency
is present in about 50% of newborns and is the main cause of
dramatically reduced survival with a mortality rate of 30–40%
(103). Infants who survive will typically reach their motor and
cognitive milestones with some delay but might be able to walk
independently. Similarly to DM1, a distal weakness is typical in
CDM and a proximal involvement indicates a poor prognosis
(104). Besides muscular symptoms, cognitive impairment, and
neuropsychological disorders are the most common and vari-
able manifestations in CDM. Symptoms range from intellectual
impairment to selective cognitive impairment, apathy, and
autism, as well as impaired attention, severe anxiety, and mood
and depression syndromes (3, 102, 105–107). In the course of the
disease, patients might require special schooling. In their third
and fourth decades, patients may develop secondary complica-
tions, such as severe contractures, scoliosis, and worsening of
cardiorespiratory symptoms (4).

CHILDHOOD/JUVENILE ONSET DM1
The childhood and juvenile onset DM1 echoes the broad overlap-
ing spectrum of symptoms of the congenital and the adult pheno-
types. Commonly, there is an expansion of CTG-repeats of more
than 800 repeats. First clinical symptoms may become apparent at
age 1–10 for childhood onset and at age 10–20 for juvenile onset
(3). Neurocognitive symptoms such as learning disability and
learning difficulties are often prominent at age around 10 years
and may become earlier apparent than muscular symptoms
(107). In contrast to CDM, prenatal abnormalities or muscular
symptoms right after delivery (neonatal hypotonia, sucking and
swallowing difficulties and secondary dysmorphic features) are
not typical, but a mild facial weakness or subtle facial dysmoria
may occur (3, 108). Early motor development is normal or only
slightly delayed. Principal complaints in early childhood are
speech and learning difficulties because of a mental handicap.
At school, learning difficulties may become apparent and sometimes
require special education. A study on 28 childhood-DM-patients
showed that the full-scale IQ was significantly decreased (73.6)
and 68% of the patients had repeated at least one school grade.
54% had additional psychiatric symptoms such as anxiety disor-
der, mood disorder, and attention-deficit-hyperactivity disorder
(107). In adolescence, patients may show typical muscular and
non-muscular symptoms of adult-onset DM1, e.g., like distal
weakness, clinical myotonia, or gastrointestinal symptoms.
Cardiologic symptoms, such as cardiac arrhythmias or cardio-
myopathy, may occur, also leading to severe complications and
sudden death (83). Life expectancy is not necessarily reduced,
as long as core symptoms are recognized and treated sufficiently.

CONCLUSION
Myotonic dystrophies represent the most variable clinical
phenotypes, so treatment stratification is key for any modern
therapeutic approach. We still need much more understanding
of the signs and symptoms of DM patients in correlation to their
molecular origins.

AUTHOR CONTRIBUTIONS
SW: review of publications, writing, critical revision of manuscript
for intellectual content, and final approval of the manuscript. FM:
review of publications, writing, and critical revision of manu-
script for intellectual content. BS: critical revision of manuscript
for intellectual content.
42. Caillet-Boudin ML, Fernandez-Gomez FJ, Tran H, Dhaenens CM, Buee L, Sergeant N. Brain pathology in myotonic dystrophy: when tauopathy meets spongiosis and RNAopathy. *Front Mol Neurosci* (2014) 6:57. doi:10.3389/fmoln.2013.00057

43. Goodwin M, Mohan A, Batra R, Lee KY, Charizanis K, Fernandez Gomez FJ, et al. MBNL sequestration by toxic RNAs and RNA mislocalizing in the myotonic dystrophy brain. *Cell Rep* (2015) 12(7):1159–68. doi:10.1016/j.celrep.2015.07.029

44. Toth A, Lovadi E, Komoly S, Schwarcz A, Orsi G, Perlaki G, et al. Cortical involvement during myotonia in myotonic dystrophy: an fMRI study. *Acta Neurol Scand* (2015) 132(1):65–72. doi:10.1111/ane.12560

45. Zanigni S, Evangelisti S, Giannoccoro MP, Oppi E, Poda R, Giorgio A, et al. Relationship of white and gray matter abnormalities to clinical and genetic features in myotonic dystrophy type 1. *NeuroImage Clin* (2016) 11:678–85. doi:10.1016/j.nicl.2016.04.012

46. Andersen G, Orregreen MC, Preisler N, Colding-Jorgensen E, Clausen T, Duno M, et al. Muscle phenotype in patients with myotonic dystrophy type 1. *Musc Nerve* (2015) 47(3):409–15. doi:10.1002/mus.23535

47. Högrel JY, Ollivier G, Ledoux I, Hebert LJ, Eymard B, Puymirat J, et al. Relationships between grip strength, myotonia, and CTG expansion in myotonic dystrophy type 1. *Ann Clin Transl Neurol* (2017) 4(12):921–5. doi:10.1002/acn3.496

48. Cardani R, Giagnacovo M, Botta A, Rinaldi F, Morgante A, Udd B, et al. Co-segregation of DM2 with a recessive CLCN1 mutation in juvenile onset of myotonic dystrophy type 2. *J Neurol* (2012) 259(10):2090–9. doi:10.1007/s00415-012-6462-1

49. Bugiardini E, Rivolta I, Binda A, Soriano Caminero A, Cirillo F, Cinti A, et al. SCN4A mutation as modifying factor of myotonic dystrophy type 2 phenotype. *Neuromuscul Disord* (2015) 25(4):301–7. doi:10.1016/j.nmd.2015.01.006

50. Rakoczy-Stojanovic V, Peric S, Paunic T, Pesovic J, Vujnic M, Peric M, et al. Quality of life in patients with myotonic dystrophy type 2. *J Neurol Sci* (2016) 365:158–61. doi:10.1016/j.jns.2016.04.018

51. Suokas KL, Haapamaa M, Kaitiainen H, Udd B, Hietaharju AJ. Pain in patients with myotonic dystrophy type 2: a postal survey in Finland. *Muscle Nerve* (2012) 45(1):70–4. doi:10.1002/mus.22249

52. Mosshourab R, Palada V, Grunwald S, Grieben U, Lewin GR, Spuler S. A molecular signature of myalgia in myotonic dystrophy 2. *Ebiomdecine* (2016) 7:205–11. doi:10.1016/j.ebiom.2016.03.017

53. Reardon W, Newcombe R, Fenton I, Sibert J, Harper PS. The natural history of congenital myotonic dystrophy: mortality and long term clinical aspects. *Arch Dis Child* (1993) 68(2):177–81. doi:10.1136/adc.68.2.177

54. Boentert M, Wenninger S, Sansone VA. Respiratory involvement in neuro muscular disorders. *Curr Opin Neurol* (2015) 28(5):432–42. doi:10.1097/WCN.0000000000000470

55. Sansone VA, Gagnon C. 207th ENMC Workshop on chronic respiratory muscular disorders. *Sleep Med* (2016) 32:92–6. doi:10.1016/j.sleep.2016.12.005

56. Itoh K, Mitani M, Kawamoto K, Futamura N, Funakawa I, Innai K, et al. Neuroophatology does not correlate with regional differences in the extent of expansion of CTG repeats in the brain with myotonic dystrophy type 1. *Acta Histochem Cytochem* (2010) 43(6):149–56. doi:10.1016/j.ahc.2010.01.009

57. Ekstrom AB, Tulinius M, Sjostrom A, Aring E. Visual function in congenital and childhood myotonic dystrophy type 1. *Opthalmolology* (2010) 117(5):976–82. doi:10.1093/ophthal.oph.2010.01.055

58. Brunner HG, Nillesen W, van Oost BA, Jansen G, Wieringa B, Ropers HH, et al. Presymptomatic diagnosis of myotonic dystrophy. *J Med Genet* (1992) 29(11):780–4. doi:10.1136/jmg.29.11.780

59. Kidd A, Turnpenny P, Kelly K, Clark C, Church W, Hutchinson C, et al. Ascertaining of myotonic dystrophy through cataract by selective screening. *J Med Genet* (1995) 32(7):519–23. doi:10.1136/jmg.32.7.519

60. Rakoczy-Stojanovic V, Peric S, Pesovic J, Sencanin I, Bozic M, Skivcic S, et al. Genetic testing of individuals with pre-senile cataract identifies patients with myotonic dystrophy type 2. *Eur J Neurol* (2017) 24(11):c79–80. doi:10.1111/ene.13401

61. Sato S, Nakamura M, Cho DH, Tapcott SJ, Ozaki H, Kawakami K. Identification of transcriptional targets for SiXS: implication for the pathogenesis of myotonic dystrophy type 1. *Hum Mol Genet* (2002) 11(9):1045–58. doi:10.1093/hmg/11.9.1045

62. Rhodes JD, Lott MC, Russell SL, Moulton V, Sanderson J, Wormstone IM, et al. Activation of the innate immune response and interferon signalling in myotonic dystrophy type 1 and 2 cataracts. *Hum Mol Genet* (2012) 21(4):852–62. doi:10.1093/hmg/ddr515

63. Shao D, Zhu X, Sun W, Hoo L, Chen W, Wang H, et al. Investigation of the molecular mechanisms underlying myotonic dystrophy types 1 and 2 cataracts using microRNA target gene networks. *Mol Med Rep* (2017) 16(4):3737–44. doi:10.3892/mmr.2017.7059

64. Passeri E, Bugiardini E, Sansone VA, Valaperta R, Costa E, Ambrosi B, et al. Vitamin D, parathyroid hormone and muscle impairment in myotonic dystrophies. *J Neurol Sci* (2013) 331(1–2):132–5. doi:10.1016/j.jns.2013.06.008

65. Terracciano C, Rastelli E, Morello M, Celi M, Bucci E, Antonini G, et al. Vitamin D deficiency in myotonic dystrophy type 1. *J Neurol* (2013) 260(9):2330–40. doi:10.1007/s00415-013-6984-1

66. Dahlqvist JAN, Orregreen MC, Wittig N, Vising J. Endocrine function over time in patients with myotonic dystrophy type 1. *Eur J Neurol* (2015) 22(1):116–22. doi:10.1111/ene.12542

67. Matsumura T, Iwashashi H, Funahashi T, Takahashi MP, Sato T, Yasui K, et al. A cross-sectional study for glucose intolerance of myotonic dystrophy. *J Neurol Sci* (2009) 276(1–2):60–6. doi:10.1016/j.jns.2008.08.037

68. Thornton CA, Griggs RC, Moxley RT III. Myotonic dystrophy with no trinucleotide repeat expansion. *Ann Neurol* (1994) 35(3):269–72. doi:10.1002/ana.410350305
81. van Vliet J, Tieleman AA, van Engelen BGM, Bassez G, Servais I, Behin A, et al. Hearing impairment in patients with myotonic dystrophy type 2. Neurology (2018) 90(7):e565–76. doi:10.1212/WNL.0000000000005303
82. Pisani V, Tirabasso A, Mazzone S, Terracciano C, Botta A, Novelli G, et al. Early subclinical cochlear dysfunction in myotonic dystrophy type 1. Eur J Neurol (2011) 18(12):1412–6. doi:10.1111/j.1468-1331.2011.03470.x
83. Bassez G, Lazarus A, Desguerre I, Varin J, Laffont P, Becane HM, et al. Severe cardiac arrhythmias in young patients with myotonic dystrophy type 1. Neurology (2004) 63(10):1939–41. doi:10.1212/01.WNL.0000144343.91136.CF
84. Wahbi K, Algalarondo V, Becane HM, Fressart V, Beldjord C, Azibi K, et al. Brugada syndrome and abnormal splicing of SCN5A in myotonic dystrophy type 1. Arch Cardiovasc Dis (2013) 106(12):635–43. doi:10.1016/j.acvd.2013.08.003
85. Sansone VA, Brigonzi E, Schoser R, Villani S, Gaeta M, De Ambrogi G, et al. The frequency and severity of cardiac involvement in myotonic dystrophy type 2 (DM2): long-term outcomes. Int J Cardiol (2013) 168(2):1147–53. doi:10.1016/j.ijcard.2012.11.076
86. Chong-Nguyen C, Wahbi K, Algalarondo V, Becane HM, Radvanyi-Hoffman H, Arnaud P, et al. Association between mutation size and cardiac involvement in myotonic dystrophy type 1: an analysis of the DM1-Heart Registry. Circ Cardiovasc Genet (2017) 10(3):e001526. doi:10.1161/CIRCGENETICS.116.001526
87. Yoshida K, Aburakawa Y, Suzuki Y, Kuroda K, Kimura T. The frequency and risk factors for ischemic stroke in myotonic dystrophy type 1 patients. J Stroke Cerebrovasc Dis (2018) 27(4):914–8. doi:10.1016/j.jstrokecerebrovasdis.2017.10.030
88. Ronnemaa T, Alaranta H, Viikari J, Tilvis R, Falck R. Increased activity of serum gamma-glutamyltransferase in myotonic dystrophy. Acta Med Scand (1987) 222(3):267–73. doi:10.1111/j.0954-6820.1987.tb10669.x
89. Kalafateli M, Triantos C, Tsamandas A, Kounadis G, Labropoulou-Karatza C. Abnormal liver function tests in a patient with myotonic dystrophy type 1. Ann Hepatol (2012) 11(1):130–3.
90. Brunner HG, Hamel BC, Rieu P, Howeler CJ, Peters FT. Intestinal pseudo-obstruction in myotonic dystrophy type 1. Am J Med Genet B Neuropsychiatr Genet (2009) 147B(6):918–26. doi:10.1002/ajmg.b.30698
91. Douniol M, Jacquette A, Guile JM, Tanguy ML, Angeard N, Heron D, et al. Psychiatric and cognitive phenotype in children and adolescents with myotonic dystrophy. Eur Child Adolesc Psychiatry (2009) 18(12):705–15. doi:10.1007/s00787-009-0037-4
92. Douniol M, Jacquette A, Cohen D, Bodeau N, Rachidi L, Angeard N, et al. Psychiatric and cognitive phenotype of childhood myotonic dystrophy type 1. Dev Med Child Neurol (2012) 54(10):905–11. doi:10.1111/j.1469-8749.2012.04379.x
93. Schara U, Schoser BG. Myotonic dystrophies type 1 and 2: a summary on current aspects. Semin Pediatr Neurol (2006) 13(2):71–9. doi:10.1016/j.spen.2006.06.002

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