Myotonic Dystrophy

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: **Myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) are genetic disorders affecting skeletal and smooth muscle, heart, brain, eyes, and other organs. The multisystem involvement and disease variability of myotonic dystrophy have presented challenges for clinical care and research. This article focuses on the diagnosis and management of the disease. In addition, recent advances in characterizing the diverse clinical manifestations and variability of the disease are discussed.**

RECENT FINDINGS: **Studies of the multisystem involvement of myotonic dystrophy, including the most lethal cardiac and respiratory manifestations and their molecular underpinnings, expand our understanding of the myotonic dystrophy phenotype. Advances have been made in understanding the molecular mechanisms of both types of myotonic dystrophy, providing opportunities for developing targeted therapeutics, some of which have entered clinical trials in DM1.**

SUMMARY: **Continued efforts focus on advancing our molecular and clinical understanding of DM1 and DM2. Accurately measuring and monitoring the diverse and variable clinical manifestations of myotonic dystrophy in clinic and in research is important to provide adequate care, prevent complications, and find treatments that improve symptoms and life quality.**

INTRODUCTION

Myotonic dystrophy comprises myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2). The two forms of the disease are genetically distinct. DM1 is caused by an expanded CTG triplet in *DMPK* on chromosome 19,[1] while DM2 is caused by the expansion of a CCTG tetramer in *CNBP* on chromosome 3.[2] Both disorders share important pathomechanistic features, resulting in many clinical similarities. The expanded DNA is transcribed into expanded RNA in both forms, which interferes with cellular mechanisms that control RNA biogenesis and gene expression. *DMPK* and *CNBP* are expressed in several different tissue types (eg, skeletal and smooth muscle, cardiac, central nervous system [CNS], eye) which result in a multisystem disease in both forms of myotonic dystrophy.

EPIDEMIOLOGY

The prevalence of myotonic dystrophy varies globally. For example, a genetic screen in Finnish blood donors revealed a similar frequency of DM1 and DM2 of 1

CITE AS:
CONTINUUM (MINNEAP MINN) 2022;28(6, MUSCLE AND NEUROMUSCULAR JUNCTION DISORDERS):1715–1734.

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RELATIONSHIP DISCLOSURE:
Dr Hamel has has received personal compensation in the range of $500 to $4999 for serving as a consultant for Vertex Pharmaceuticals.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Hamel discusses the unlabeled/investigational use of mexiletine for the treatment of myotonia and modafinil for the treatment of daytime sleepiness in myotonic dystrophy.

in 2260.[3] The prevalence is even higher in certain areas, in part due to genetic founder effects; for example, in northern Quebec, the prevalence is 1 in 550 for DM1.[4] In the US, a recent genetic screen of anonymized blood spots showed that 1 in 2100 newborns in New York state carried the DM1 mutation.[5]

Clinical experience suggests that DM2 is less common than DM1 in the US. However, the neuromuscular signs of DM2 often emerge after age 45, and frequently a long diagnostic delay occurs,[6-8] making it likely that DM2 is underdiagnosed. In support of this idea, a recent Serbian study of 151 patients with cataracts before age 55 showed that 7.2% carried an unsuspected DM2 mutation, with some patients showing signs of an unrecognized myopathy.[9]

GENETICS

The myotonic dystrophies are autosomal dominant repeat expansion disorders. The expanded repeats in both types of myotonic dystrophy are located in noncoding regions. In DM1 the CTG triplet is in the 3' untranslated region of *DMPK*,[1] a gene encoding a protein kinase, whereas in DM2 the expansion of a CCTG tetramer is in the first intron of *CNBP,* encoding a nucleic acid binding protein.[2] As no functional connections are known between these genes, the shared clinical features are believed to reflect similar biochemical properties and toxicities of the respective RNA repeats, in terms of propensity to interact with particular RNA binding proteins. On the other hand, the gene of origin is not irrelevant since gene expression patterns determine which cells and organs are susceptible to developing a phenotype.

Genetic Basis of Disease Heterogeneity

Although clinical heterogeneity is ubiquitous in genetic disorders, it is particularly extreme in DM1. In a single family of DM1, the age of onset often ranges from in utero to after the sixth decade. Earlier onset is associated with greater disease severity. The disease spectrum in DM2 is not as wide but still ranges from asymptomatic individuals with minimal signs of disease to loss of ambulation. However, DM2 has no congenital form.

The following are some of the genetic concepts that underlie disease variability and that are relevant for genetic counseling in the clinic.

PROGNOSTIC VALUE OF REPEAT LENGTH AND DISEASE SEVERITY. In DM1, patients have at least 50 to more than 1000 CTG repeats in blood cells compared to fewer than 37 repeats in people without DM1. In DM2, the number of CCTG repeats in blood cells ranges from 75 to 10,000 with an average of 5000, compared to 11 to 26 repeats in normal alleles. Initial studies of smaller cohorts in DM1 suggested that the longer the repeat size, the earlier symptoms develop and the more severe the disease.[10] However, in recent larger studies repeat length as measured in blood cells only explained 17% to 22% (compared to 65%) of the variability in age of onset in DM1.[11,12] Moreover, it is also becoming clear that size is not the only characteristic of the CTG repeat tract that affects symptoms. Up to 8% of patients with DM1 have sequence interruptions near the downstream end of the CTG repeat tract, in which one or more CTG units are replaced by CCG or CGG triplets.[11] Studies suggest that interruptions tend to stabilize repeats, which is associated with an overall reduction of disease severity or, in some cases, qualitatively different symptoms.[13,14] Notably, some commercial labs provide binary results (positive/negative) for myotonic dystrophy genetic tests or a range

for repeat length, and repeat interruptions are uniformly not assessed. In addition, blinded performance tests have shown substantial variability of repeat size measurements in commercial laboratories when identical samples were analyzed in different runs.[15] For all these reasons, clinicians and genetic counselors should remain cautious about prognostic counseling based on CTG repeat size. Even the general rule that congenital-onset DM1 is associated with large CTG expansions (>750 repeats) has apparent exceptions.[16] Correlations of disease severity and repeat length in blood cells have not been shown for DM2. While the underlying mechanisms of disease variability in DM2 remain uncertain, it is possible that individual differences in the metabolism of RNA from the expanded *CNBP* allele may play an important role.[17] Also, case reports suggest that concomitant mutations in *SCN4A* and *CLCN1* genes may occasionally act as disease modifiers, presumably by affecting the severity of myotonia.[18,19]

REPEAT INSTABILITY. When the repeat sequence is expanded, it becomes remarkably unstable. For example, when DM1 repeat expansions are passed from one generation to the next they tend to increase in size, often resulting in earlier disease onset, a phenomenon known as *anticipation* (CASE 8-1). Contractions may also occur but are less common. Anticipation and intergenerational expansion in DM2 are much less conspicuous than in DM1. The repeat is also unstable in somatic cells (ie, somatic instability). In DM1, CTG repeat expansions strongly tend to increase in size over time, but at different rates in different tissues. For example, expanded CTG repeats in leucocytes enlarge slowly over time and become more heterogeneous. In other tissues, including nonproliferating cells such as skeletal muscle, heart, and brain, the tissues with the highest *DMPK* expression, the age-related increase can lead to repeat sizes of 2000 to 5000.[20] Factors determining these cell- and tissue-specific differences are currently unknown. It seems likely that age-dependent changes of repeat length are key determinants of symptom onset, phenotypic variability, and disease progression. Somatic instability is less studied in DM2.

GENDER-SPECIFIC TRANSMISSION OF MYOTONIC DYSTROPHY. The most severe form of myotonic dystrophy, myotonic dystrophy with congenital onset (congenital myotonic dystrophy), is typically passed on by mothers with DM1, as large intergenerational expansions are more likely to occur with maternal transmission.[21-24] However, a recent French study reported an unexpectedly high rate of paternal transmission of congenital myotonic dystrophy (12.7%).[16] In childhood-onset myotonic dystrophy, paternal and maternal transmission rates are similar. The underlying mechanism of gender-specific transmission in congenital myotonic dystrophy is not fully understood. Maternal-specific epigenetic mechanisms during germline formation have been suggested, resulting in abnormal methylation of the DM1 locus.[24,25]

MAKING THE DIAGNOSIS OF MYOTONIC DYSTROPHY

If clinical suspicion exists for DM1 or DM2, obtaining genetic confirmation is the next step. In most cases, DM1 and DM2 can be clinically distinguished, and testing for one condition is sufficient. Genetic counseling of patients is important to explain the autosomal dominant inheritance pattern and risks to

KEY POINTS

- Myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) are autosomal dominant diseases due to expanded CTG repeats in *DMPK* (DM1) and CCTG repeats in *CNBP* (DM2). While genetically distinct, both diseases share many mechanistic and clinical features, such as myopathy, myotonia, and multisystem disease.
- Both types of myotonic dystrophy are caused by toxic foci of expanded (C)CUG repeats that sequester RNA-binding proteins. Depletion of these RNA-binding proteins results in the missplicing of transcripts from several genes.
- A recent screen of 50,382 consecutive births showed that 1 in 2100 individuals carries the DM1 mutation in the US. DM2 is considered less common, but likely overlooked and underdiagnosed.
- Disease variability is a hallmark of DM1 and is present but less pronounced in DM2. In DM1, the age of symptom onset ranges from in utero to after the sixth decade. Earlier onset is typically associated with more severe disease. No congenital form of DM2 exists.
- The genetic determinants of disease variability are not well understood in DM1. Clinicians and genetic counselors should remain cautious or refrain from prognostic counseling based on CTG repeat size.

offspring, including the risk of having a child with congenital myotonic dystrophy. EMG shows myopathy and electrical myotonia, which is spontaneous discharges of waxing and waning amplitude and frequency and is often compared to the audio of a "dive bomber," but this can be less prominent and prevalent in DM2. Electrical myotonia without clinical myotonia can be seen in a variety of muscle diseases.[26] Muscle pathology shows a myopathy typically with abundant pyknotic clumps and many central nuclei. However, muscle pathology is not needed to make the diagnosis. In addition, although pathologic features can be supportive, they are not pathognomonic for myotonic dystrophy.

CASE 8-1

A 22-year-old woman was referred for neuromuscular consultation after electrical myotonia was detected by EMG on a study ordered to evaluate for carpal tunnel syndrome. The patient and her mother reported that she had developed trouble speaking since age 14, and sometimes needed to repeat herself or slow her speech so that people could understand her. Since elementary school, she napped every day despite sleeping an average of 14 hours a day, and she struggled to keep a schedule. She had alternating constipation and diarrhea and spent at least 2 hours a day in the bathroom. The patient had been previously diagnosed with a learning disability, speech impediment, and irritable bowel syndrome and underwent extensive, fruitless diagnostic workups. Her trouble staying awake and gastrointestinal (GI) symptoms affected her social life and academic performance. Upon questioning, the patient reported that her hand gets "stuck," specifically in the cold, since about age 12, but she did not think much of it as her older sister had reported the same.

On examination, she had an elongated face with slight temporal wasting and moderate facial weakness. She had mild dysarthria and mild weakness of finger flexors and ankle dorsiflexors. She exhibited 5 seconds of grip myotonia bilaterally, which improved with repetition.

A genetic test for the CTG repeat expansion on *DMPK* confirmed the diagnosis with 11 and 400 repeats. The patient's mother reported cataracts at age 58 but no other symptoms, and her genetic test showed 80 CTG repeats.

COMMENT

This patient reported mild muscle symptoms of myotonic dystrophy type 1 (DM1) in her limbs, had moderate facial weakness, and struggled with significant GI and sleep disturbances and a learning disability. Her presentation was consistent with juvenile-onset DM1. The multisystem symptoms she struggled with for years have a unifying explanation. GI symptoms can be challenging to manage, but medical, dietary, and behavioral interventions should be implemented. She also required a sleep study and pulmonary function testing, given her excessive daytime sleepiness and increased sleep requirement. It was also important for the patient, but also her mother to have a cardiac evaluation to evaluate for conduction abnormalities, despite her mother's minimal disease burden.

MOLECULAR PATHOMECHANISM

DMPK and *CNBP* alleles containing repeat expansions are transcribed into RNA. The transcripts with expanded repeats (ie, CUG repeats in DM1, CCUG repeats in DM2) (FIGURE 8-1) are retained in the nucleus in discrete foci. Within these foci, the mutant RNA sequesters RNA-binding proteins in the Muscleblindlike (MBNL) family. MBNL proteins are RNA-binding proteins that regulate alternative splicing of pre-mRNAs. Sequestration of these proteins results in missplicing of several MBNL-dependent pre-mRNAs. For example, missplicing of the *CLCN1A* gene transcript, which codes for a chloride channel, causes muscle myotonia,[27] and missplicing of the *INSR* gene transcript, which codes for an insulin receptor, results in diabetes (FIGURE 8-1).[28] Missplicing of *SCN5A* mRNA, which codes for a subunit of the cardiac voltage-gated sodium channel, was recently found in DM1 heart muscle.[29] In DM1 muscle tissue, a set of abnormally spliced mRNAs is correlated with muscle weakness[30] and serves as a biomarker in therapeutic trials (NCT02312011 and NCT05027269).

The larger repeat size in DM2 would be expected to titrate more MBNL proteins, resulting in greater splice alterations and disease severity. Indeed, RNA foci were more intense in DM2 muscle compared to DM1.[31] Paradoxically, DM2 occurs later in life with no congenital form and a generally favorable disease course. A recent study demonstrated that Rbfox RNA-binding proteins, which regulate RNA metabolism, competitively bind to CCUG repeats, releasing MBNL

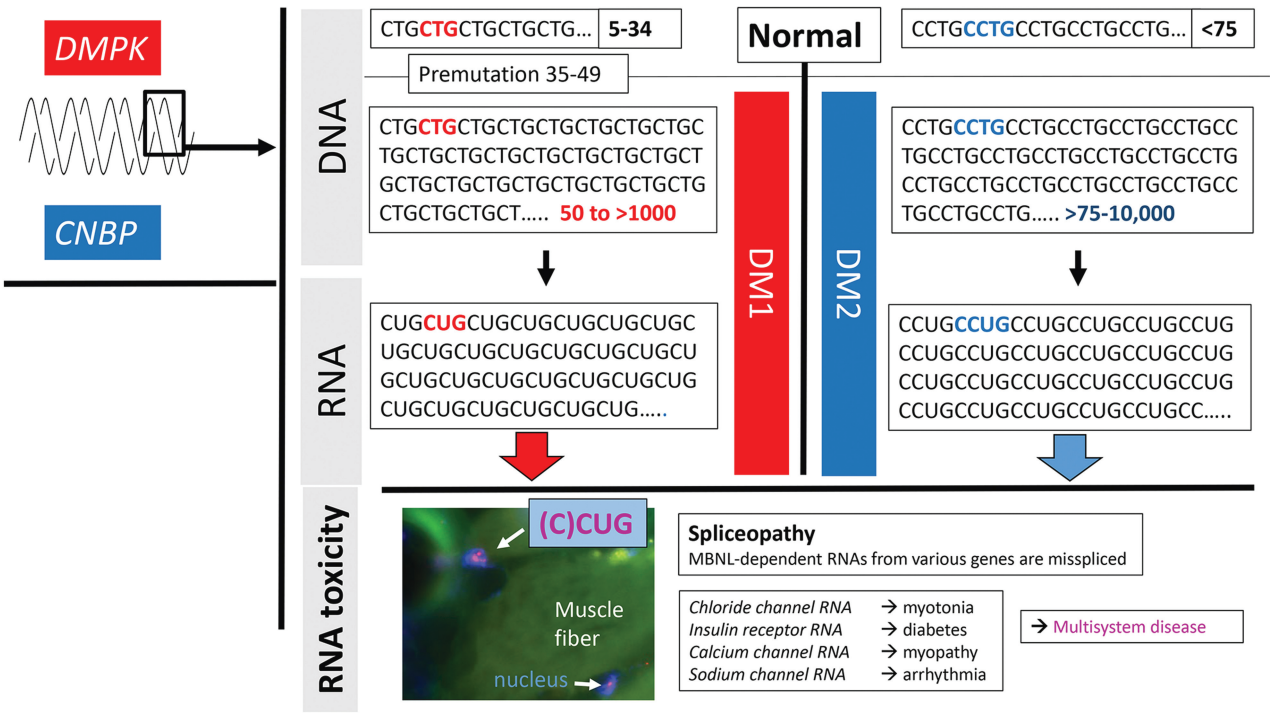

FIGURE 8-1

Myotonic dystrophy genetics and mechanism. Transcripts of expanded repeats form nuclear foci and sequester RNA-binding proteins, primarily of the muscleblindlike (MBNL) family, resulting in functional MBNL depletion and a spliceopathy by missplicing of several MBNL-dependent transcripts.

DM1 = Myotonic dystrophy type 1; DM2 = Myotonic dystrophy type 2.

proteins.[32] This evidence suggests that Rbfox proteins may play an important role in reducing RNA toxicity in DM2 and might help explain the milder phenotype.

Studies demonstrated that the disease mechanism active in muscle also operates in the brain.[33,34] Nuclear foci were observed in DM1 cortical neurons, hippocampus, thalamus, hypothalamus, and brainstem. Splicing alterations in brain tissue suggested that MBNL sequestration is also a major driver of missplicing in the brain.[33,35] Another mechanism discovered in the brains of patients with DM2 involves translation that is initiated within the repeat tract resulting in toxic peptides, referred to as repeat-associated non-AUG (RAN) translation.[36,37]

CLINICAL SPECTRUM AND MANAGEMENT OF MYOTONIC DYSTROPHY TYPES 1 AND 2

For clinical and research purposes it is useful to subdivide DM1 into different categories of disease severity.

Congenital Myotonic Dystrophy and Childhood Myotonic Dystrophy Type 1

Congenital myotonic dystrophy is the most severe form of DM1 and is defined by the presence of symptoms within the first month of life. Prenatal symptoms can include decreased fetal movements (in 33% to 38%) and polyhydramnios (in 47% to 58%).[23] Symptoms at birth involve hypotonia, respiratory weakness, feeding difficulties, and skeletal deformities (eg, clubfeet). A recent study of 38 individuals with congenital myotonic dystrophy ascertained through a Canadian national surveillance program showed that prematurity occurred in 36% and Caesarean sections were performed in 41%. Apgar scores of 6 or less were reported in 52% of patients at 5 minutes. Seventy-two percent required ventilator support for respiratory weakness in the neonatal period, and 77% required feeding therapy due to sucking or swallowing difficulties, with 68% requiring feeding therapy for longer than 14 days.[23] Children with congenital myotonic dystrophy were at the greatest risk of death in the neonatal period (16%), mostly due to respiratory failure. The leading cause of morbidity in the first 5 years of life was respiratory tract infections.[23]

A French cross-sectional study included 155 patients with congenital myotonic dystrophy of varying ages before adulthood. Orofacial weakness was most common (83%), while myotonia was less prevalent (55%) and rarely severe. Foot deformities were present in 73%. Less than 4% of patients were unable to walk. Neurodevelopmental alterations were common, affecting slowed processing, attention deficit, and language disorders.[16] Patients with congenital myotonic dystrophy often fulfill the criteria for an autism spectrum disorder (49%).[38] Children with congenital myotonic dystrophy have delayed milestones, but motor symptoms typically improve in early childhood.[39] While cognitive impairment and orofacial weakness are the prominent features early on,[40] patients with congenital myotonic dystrophy develop weakness consistent with a more adult-onset myotonic dystrophy phenotype later in life.

Patients with symptom onset after 4 weeks and before age 10 are considered to have infantile or childhood onset, while symptom onset between ages 10 and 18 has been referred to as juvenile onset (CASE 8-1). A study of 126 patients with the childhood and juvenile forms revealed a continuum of neurodevelopmental alterations and facial hypotonia, which are more severe with earlier age of onset.[16] Musculoskeletal impairment was mild, with severe grip myotonia found

less often in childhood-onset myotonic dystrophy (16%) and light grip myotonia present in about half of all children with noncongenital DM1.

Adult-Onset Myotonic Dystrophy Type 1

DM1 is often recognized through its characteristic patterns of muscle involvement, in which cranial, oropharyngeal, trunk, and distal limb muscles are preferentially affected (FIGURE 8-2). Weakness and atrophy of the jaw and facial muscles (temporal wasting) results in a narrow facial contour and reduced facial expression. Oropharyngeal weakness results in dysarthria and dysphagia. Patients have trouble lifting their heads in bed due to neck flexion weakness. Weakness of neck extensors and truncal muscles can result in a head drop and camptocormia. Hand function is affected by myotonia, delayed relaxation of muscles, and weakness of forearm and hand muscles. Myotonia results in difficulty releasing a grip, such as when shaking hands or letting go of a doorknob. Myotonia can also affect the tongue or jaw, which can impact speech and chewing. Myotonia often worsens in cold temperatures. Hand weakness manifests as difficulty opening cans or bottles or buttoning shirts. Distal leg weakness manifests as foot drop (weakness of ankle dorsiflexors) or difficulty walking, climbing stairs, or running (plantarflexion weakness).

Recent studies have emphasized that gait instability, falls, and fractures are important sources of morbidity in DM1. Falls were reported by 30% of patients within the past 6 months, and fractures by 6% to 11%.[41] In a study of 43 patients, 77% reported at least one fall at 5 years follow-up, along with an increased fear of falling and avoidance of activities to minimize fall risk.[42] Proximal muscles are typically involved later in the disease course and result in difficulty rising from a chair or with activities above the head.

KEY POINTS

- The expanded CTG repeat in DM1 grows over time in different tissues at different rates (somatic instability). For example, while the repeat remains relatively stable in leucocytes, the repeat expands remarkably over time in clinically preferentially affected tissues, such as muscle.
- The most severe form of DM1, congenital myotonic dystrophy, mostly occurs via maternal transmission.
- Characteristic muscle features of DM1 are weakness of distal limb muscles prominently affecting finger flexors, neck flexion, orofacial, pharyngeal, and respiratory muscles, as well as grip and percussion myotonia.

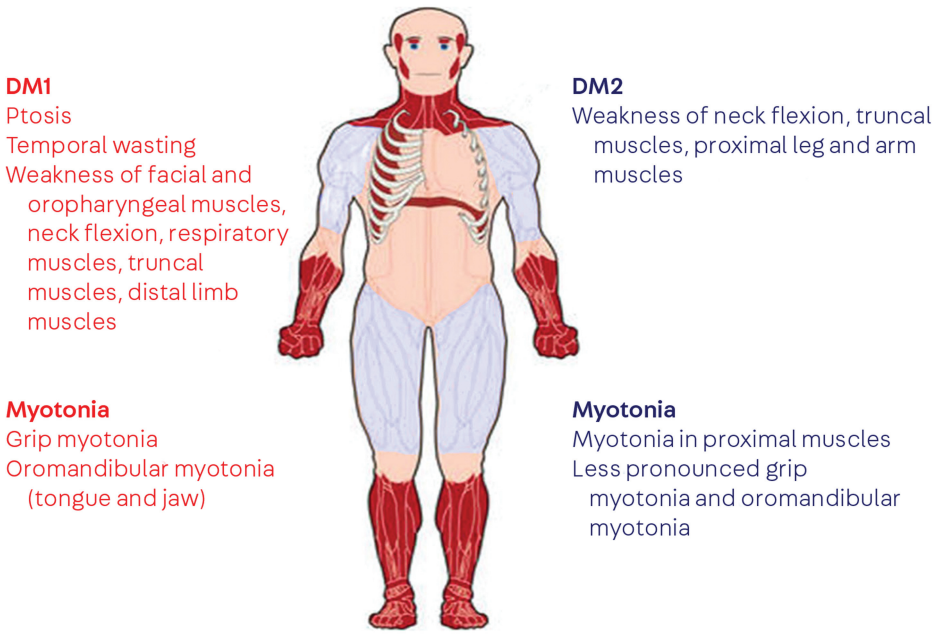

FIGURE 8-2
Preferential distribution of muscle weakness in myotonic dystrophy.
DM1 = Myotonic dystrophy type 1; DM2 = Myotonic dystrophy type 2.

Fatigue is a common symptom in myotonic dystrophy, but a set of questions is required to identify which of the various sources of fatigue the patient may be referring to.

In myotonic dystrophy, patients can experience apathy (lack of motivation) and excessive daytime sleepiness (see Respiratory and Sleep Phenotypes section), but also experience fatigue as a delayed recovery following exercise or activity.

On physical examination, weakness of neck flexion (tested supine) and finger flexors are often the first signs of myopathy. Handgrip myotonia is often pronounced early in the disease course of DM1 and becomes less prominent as hand weakness progresses. Percussion myotonia can be elicited by percussion of the finger extensor or thenar eminence with subsequent prolonged muscle contraction.

MANAGEMENT OF MOTOR SYMPTOMS IN MYOTONIC DYSTROPHY TYPE 1. In the absence of targeted treatments for muscle weakness, care focuses on maximizing safety and function. Assistive and adaptive devices such as ankle braces, canes, or walkers can augment mobility and safety. Physical and occupational therapy assessments are important, as is evaluation by a speech and swallow therapist.

EXERCISE IN MYOTONIC DYSTROPHY TYPE 1. Exercise is viewed with caution in muscular dystrophies, particularly when the mutation affects proteins involved in muscle integrity. However, in DM1 and DM2 the causal mutation does not affect muscle integrity and is not located in a coding region, but rather is due to toxic RNA gain of function (see previous Molecular Pathomechanism section). Smaller studies have shown that low- to moderate-intensity aerobic and resistance exercise is safe and can improve function in DM1.[43-45] Therefore, low- to moderate-intensity aerobic exercise is typically recommended, along with avoiding sedentary lifestyles as much as possible. However, given the marked variability of the disease, individual exercise plans are best reviewed with a physical therapist and the patient's treatment team. The mechanism as to why exercise may be particularly beneficial in DM1 is not clear yet, but studies in transgenic animal models of DM1 suggest a beneficial effect of aerobic exercise by improving splicing dysregulation and muscle function.[46-48] A recent study in 11 individuals with DM1 involving muscle biopsies before and after the intervention showed that a 12-week aerobic exercise program caused improvement of aerobic capacity and mobility, but not by the mechanism observed in transgenic mice.[49] Future research involving larger samples may help identify the best exercise modality and intensity and further elucidate the underlying mechanisms of exercise effects.

A multicenter randomized controlled trial in patients with DM1 with severe fatigue showed a positive effect of cognitive-behavioral therapy on activity level and social participation.[50] The 10-month cognitive-behavioral therapy program focused on strategies to compensate for lack of initiative, which led to increases in objective physical activity and exercise capacity, including an average 8% increase in distance walked on the 6-minute-walk test (6MWT) and decreased fatigue. In the treatment group, the frequency of reported falls was increased, potentially due to increased activity versus an increased tendency to report falls in that group.

A double-blind randomized placebo-controlled trial evaluated the effect of metformin on mobility measured by the 6MWT in 38 patients with DM1.[51] No

significant difference in distance walked between the groups was noted; however, the study had a high drop-out rate, which was greatest (>50%) in the treatment group. In the analysis, which only included subjects who completed the study (9 receiving metformin), a significant distance (7%) was gained on the 6MWT. The small sample size, risk of selection bias, and the possibility that patients may have become unblinded due to gastrointestinal side effects from metformin limit the interpretation of these results.

MYOTONIA IN MYOTONIC DYSTROPHY TYPE 1. A recent randomized, double-blind, placebo-controlled trial of mexiletine (150 mg 3 times daily) in 40 adults with noncongenital DM1 showed improvement of handgrip myotonia.[52] No differences in terms of side effects between the groups were noted. While mexiletine did not demonstrate any detrimental cardiac conduction or ventricular repolarization effects, patients with second- or third-degree heart block, atrial flutter or fibrillation, or ventricular arrhythmias were excluded from the study.[52] The author typically considers treatment with mexiletine if myotonia significantly impacts the patient's function, but obtaining an ECG prior to initiation and consulting with the patient's cardiologist is recommended. Ranolazine and lamotrigine have been tested in small studies in patients with nondystrophic myotonia, but neither drug has been tested in myotonic dystrophy.[53,54]

Myotonic Dystrophy Type 2

In DM2, the average age of onset is about 10 years later compared to DM1 and ranges from 34 to 48.[6-8,55] The first symptom is most commonly leg weakness, followed by myalgia and myotonia.[7,8,55] Symptoms involve difficulty climbing stairs or getting up from the ground (CASE 8-2). On examination, neck flexors and proximal muscles of the limb girdle are preferentially affected (FIGURE 8-2). Axial muscle weakness can occur. Later in the disease, muscle weakness progresses from proximal to distal muscles. Myotonia is variably present in proximal muscles and can manifest as stiffness with the initiation of movement following rest and as grip myotonia. Disease progression is slow, and compared to DM1, disease burden and disability is shifted toward older age.[56] The diagnostic delay is twice as long for patients with DM2 compared to DM1 (average of 12 years), possibly related to several diagnostic challenges. The pattern of weakness is not specific, a feature shared with many other acquired or genetic muscle diseases. Milder symptoms beyond the fifth decade are often initially attributed to aging. The presence of electrical myotonia can raise suspicion for DM2 but is not present in all patients. Recognition of multisystem symptoms including early cataracts can help point toward the correct diagnosis. Physical therapy assessments can assist with identifying needs for assistive devices, such as the use of a walker.

EXERCISE IN MYOTONIC DYSTROPHY TYPE 2. Exercise can worsen pain for some individuals with DM2, but also provides significant benefits for others. A recent study of 10 patients showed that a supervised combined resistance and aerobic exercise program twice a week over 16 weeks was safe and resulted in improvement of functional assessments and lean body mass.[57]

MUSCLE PAIN IN MYOTONIC DYSTROPHY TYPE 2. Many patients with DM2 experience pain and myalgia, variable across studies (50% to 80%), which can be the most disabling symptom and is often misdiagnosed initially as fibromyalgia.[58,59]

KEY POINTS

- Management of muscle symptoms includes physical therapy and the use of assistive devices. Establishing an individual and safe plan for exercise and avoiding a sedentary lifestyle are beneficial in both DM1 and DM2. Cognitive behavioral therapy can help increase activity levels and decrease fatigue in patients with DM1.
- If grip or oropharyngeal myotonia is impacting a patient's function (DM1 and DM2), mexiletine can be used if no cardiac contraindications are present.
- DM2 is characterized by symptom onset typically between ages 34 to 48. Patients live with symptoms for on average 12 years before the correct diagnosis is made.
- Initial symptoms of DM2 include leg weakness, myalgia, and myotonia. Muscle pain is common. On examination, patients reveal weakness of neck flexion and proximal muscles.

Muscle pain predominantly affects the thighs, but the upper arms, neck, back, and lower legs can also be affected (CASE 8-2).[58,60,61] Patients can experience worsening pain with palpation or pressure and in cold temperatures.[58,60,61] The underlying molecular mechanism of muscle pain in DM2 is not known and subject to further studies.[62] Specific treatments for pain in DM2 have not been systematically tested. Nonsteroidal anti-inflammatory drugs and medications treating chronic and neuropathic pain are typically tried with mixed effects. If a component of proximal myotonia is suspected to contribute to pain levels, a trial of antimyotonia medications can be considered. Statin use may exacerbate muscle pain. Regular exercise can alleviate pain in some patients and exacerbate it in others. Reviewing an individual exercise plan with regards to type and intensity of exercise with a consulting physical therapist is recommended.

Extramuscular Manifestations of Myotonic Dystrophy Types 1 and 2

The most important aspects of multidisciplinary care in myotonic dystrophy are reviewed in TABLE 8-1. Care guidelines have been published for DM1, DM2, and congenital/childhood myotonic dystrophy and provide helpful guidance in clinic.[63-65]

RESPIRATORY AND SLEEP PHENOTYPES. Excessive daytime sleepiness is common, being reported by 93% of patients with DM1, and rated as the third most bothersome symptom overall (CASE 8-1).[66] Excessive daytime sleepiness can be the result of multiple manifestations of DM1 including central or obstructive

CASE 8-2

A 40-year-old man presented with difficulty getting up from the ground and rising from a squat. For the preceding 2 years, the patient noted a burning pain in both thighs. In addition, he experienced stiffness in his legs and hips when first getting up following rest. The stiffness resolved with activity and seemed worse in the cold. The pain and stiffness were worst with inactivity, such as after a long car ride. He denied any issues with releasing a doorknob or opening his fist. He did not have cataracts, but his mother did at age 48. His mother had trouble climbing stairs in her seventh decade, which she attributed to her age. She also had two miscarriages.

Neurologic examination showed neck flexion weakness and symmetric proximal weakness in hip flexion and abduction (4/5). Action myotonia was not present, but 2 seconds of delayed relaxation upon percussion of the thenar eminence was seen.

EMG disclosed myotonic discharges in a few proximal muscles. Laboratory testing revealed a minimally elevated creatine kinase and elevated γ-glutamyl transferase (GGT) level. A genetic test confirmed an expanded repeat in *CNBP*.

COMMENT

This patient had a fairly typical presentation of DM2, including proximal muscle weakness and myalgia in the thigh muscles. His symptoms of stiffness with transitions suggested myotonia in proximal muscles.

Overview of the Most Important Multisystem Disease Manifestations in Myotonic Dystrophy Types 1 and 2 and Monitoring Recommendations[a]

TABLE 8-1

Respiratory

- DM1: for symptomatic patients, pulmonary function testing (forced vital capacity sitting and supine, peak cough flow) every 6 months; for asymptomatic patients, serial testing interval can be adjusted by the treating physician or pulmonologist
- DM2: for symptomatic patients, monitoring is the same as for DM1; for asymptomatic patients, pulmonary function testing every 2 years
- Age-appropriate vaccinations
- Caution with supplementary oxygen in the setting of hypercapnia
- Obtain pulmonary function testing preoperatively

Sleep

- Polysomnogram for excessive daytime sleepiness, erratic sleep, increased sleep requirement, and symptoms of sleep apnea

Cardiac

- ECG annually (minimum)
- Referral to cardiology if abnormal ECG or symptoms, or normal ECG and asymptomatic but over age 40[b]

Gastrointestinal

- Dysphagia: evaluation by a speech/swallowing therapist
- Assess and treat constipation, diarrhea, and gastroesophageal reflux disease and referral to a gastrointestinal specialist for refractory symptoms

Eyes

- Annual ophthalmologic examination, which should continue following cataract removal (evaluate for recurrent cataract, Fuchs endothelial corneal dystrophy)

Cancer

- Age- and sex-appropriate cancer screening, including annual dermatology evaluation
- Consider thyroid ultrasound

Metabolic derangements

- Lipid panel, thyroid-stimulating hormone (TSH) test, free thyroxine test every 3 years if normal; otherwise, more frequently or as appropriate for age
- Screening for diabetes annually

Anesthesia

- A one-page overview of anesthesia recommendations can be found at myotonic.org/sites/default/files/pages/files/MDF_PracticalSuggestionsDM1_Anesthesia2_17_21.pdf and should be shared with providers ahead of planned procedures

[a] For full care guidelines, see references.[63-65]
[b] This also applies to older adults with minimal muscle symptoms.

sleep apnea, nocturnal hypoventilation due to respiratory muscle weakness, a manifestation of CNS involvement, or a consequence of abnormal circadian rhythm regulation.

Respiratory failure related to progressive muscle weakness is the most common mechanism of death in patients with DM1. Inspiratory and expiratory muscles can be affected.[67,68] Nocturnal hypoventilation was identified in 72.2% of patients with DM1 with nonrestorative sleep and excessive daytime sleepiness.[69]

Obstructive and central sleep apnea was reported in 69% of patients with DM1, with 42% requiring treatment with noninvasive ventilation.[70] Whether subjective measurements of sleepiness or fatigue correlate with respiratory function, sleep quality, or treatment response is uncertain.[69]Abnormal pulmonary function is found in 27% of children with DM1, being most common and severe in congenital myotonic dystrophy (41%).[16]

MANAGEMENT OF EXCESSIVE DAYTIME SLEEPINESS. It is important to assess respiratory muscle function via pulmonary function testing. Measurement of forced vital capacity (FVC) is best evaluated in both sitting and supine positions to assess for a drop in FVC when supine due to diaphragmatic weakness. Peak cough flow can be useful to assess expiratory muscle strength. Sleep apnea is assessed via polysomnogram.

Treatment most commonly includes noninvasive ventilation, mainly bilevel positive airway pressure (BiPAP). Continuous positive airway pressure (CPAP) may be sufficient if isolated obstruction exists. Noninvasive ventilation significantly improves nocturnal hypoventilation without deterioration of sleep quality.[69] A prospective study of 190 patients requiring noninvasive ventilation showed that patients who decline or delay noninvasive ventilation usage are at greater risk of death and need for mechanical ventilation. Noninvasive ventilation users who used it less than prescribed had higher mortality, suggestive of a possible "dose-dependent" effect.[71] However, noninvasive ventilation is often poorly tolerated by patients with DM1, and only about one-third of patients in whom it is prescribed continue to use it.[72]

If respiratory or sleep assessments do not indicate the need for noninvasive ventilation, or patients continue to have significant symptoms despite noninvasive ventilation, stimulants such as modafinil can be considered in individuals with hypersomnolence.[73,74] However, stimulant usage in DM1 can be limited due to the risk of cardiac arrhythmias or gastrointestinal (GI) side effects.

In DM2, impaired sleep or daytime sleepiness was reported by 77% of patients.[75] Respiratory impairment has been described in 10% to 13% of patients and sleep apnea in 43%, with 2% requiring noninvasive ventilation.[55,70,75] In the US-based National Registry for Myotonic Dystrophy, the percentage of patients with DM2 reporting noninvasive ventilation use is higher (7.87%).[56]

CARDIAC EFFECTS. Cardiac involvement in DM1 and DM2 manifests as progressive conduction system disease leading to heart block and sudden death, sinus bradycardia, atrial fibrillation, or ventricular tachyarrhythmia, whereas heart failure due to cardiomyopathy is less common. A study by Wahbi and colleagues[76] using a French registry of 1388 patients reported a cumulative incidence of major conduction system disease of 19.3% at 12 years, and 56% of patients were asymptomatic, supporting the need for monitoring of the

conduction system using periodic ECGs and longer-term recordings and evaluation for pacemaker placement to prevent syncope and sudden death. Left ventricular systolic dysfunction is seen in about 10% of patients and is associated with a poor prognosis.[77-79]

In children with DM1, cardiac abnormalities occur less frequently but can be severe. Cardiac anomalies were seen in 15% of children, with 4% requiring an antiarrhythmic device.[16]

Cardiac conduction abnormalities in DM2 have been described as less common compared to DM1 (19%),[8] but with progression over time.[80] Severe cardiac abnormalities were seen in 8% of patients in a Serbian cohort.[55] Cardiomyopathy has been reported in 4% to 6%, and antiarrhythmic devices were implanted in 4% to 6%.[55,80]

Mortality in Myotonic Dystrophy Types 1 and 2

Cardiac and respiratory disease account for the reduced life expectancy in DM1. In the National Registry for Myotonic Dystrophy the median survival in individuals with DM1 who developed symptoms after age 10 is reduced at age 70 compared to the general population, although not all deaths may be reported to the registry.[56] Wahbi and colleagues[81] developed a DM1 prognostic score containing clinical information (age, diabetes, need for support when walking, heart rate, systolic blood pressure, heart block, and vital capacity). The 10-year survival rate was 96.6% in the group with the lowest score and 19.4% in the group with the highest score. The median survival in patients with DM2 in the National Registry for Myotonic Dystrophy was 80 years, concordant with general estimates for the US population.

Central Nervous System Manifestations in Myotonic Dystrophy Types 1 and 2

Compared to neuromuscular manifestations, CNS manifestations are less distinct and more severe in DM1 than in DM2. Individuals with myotonic dystrophy have variable cognitive deficits across all domains, including social cognition, memory, and visuospatial and executive function.[82] This can manifest as having trouble engaging in care, organizing, and keeping schedules. In addition to cognitive deficits, CNS manifestations include apathy and hypersomnolence.[83] Apathy has been described in 40% of patients with DM1.[84,85]

MRI studies reveal changes in white and gray matter signal intensity.[86] Further work is being conducted to better characterize the underlying CNS mechanism and to identify a reliable outcome measure or biomarker to assess CNS dysfunction.

MANAGEMENT OF CENTRAL NERVOUS SYSTEM MANIFESTATIONS IN MYOTONIC DYSTROPHY TYPES 1 AND 2. The multicenter randomized controlled trial demonstrating the positive effect of cognitive-behavioral therapy targeting strategies to compensate for lack of initiative and its effects on activity level was discussed previously.[50] The trial showed that cognitive behavioral therapy increased the capacity for activity and social participation.

Gastrointestinal Symptoms in Myotonic Dystrophy Types 1 and 2

Myotonic dystrophy affects both skeletal and smooth muscle. Gastrointestinal symptoms can affect the GI tract in its entirety, from dysphagia to sphincter

KEY POINTS

- Respiratory failure related to progressive muscle weakness is the most common mechanism of death in patients with DM1.
- Noninvasive ventilation for respiratory weakness and sleep apnea improves nocturnal hypoventilation and sleep apnea but is often not tolerated by patients.
- Cardiac involvement is the second leading cause of death in DM1. Cardiac involvement includes progressive conduction abnormalities resulting in heart block, arrhythmia, and risk of sudden death. Heart failure is less common.
- In addition to skeletal muscle, smooth muscle is affected by myotonic dystrophy. Gastrointestinal symptoms are common and include dysphagia, acid reflux, constipation, diarrhea, and sphincter dysfunction.

dysfunction (CASE 8-1). Trouble swallowing is the most common GI symptom reported by patients with DM1 (55%), followed by acid reflux (38%) and constipation (33%). Patients with DM2 most commonly report constipation (53%), followed by acid reflux (46%) and trouble swallowing (29%).[87] Other symptoms can include diarrhea, abdominal pain, and problems with defecation. Diarrhea and constipation often coexist, and individuals may have been diagnosed with irritable bowel syndrome before symptoms are recognized as part of myotonic dystrophy. Cholecystectomy is reported earlier in life in individuals with myotonic dystrophy than in the general population, more commonly in women than men, and may result from smooth muscle involvement.[88] In children with congenital and childhood onset myotonic dystrophy, constipation was present in 24% and diarrhea in 10%. Enuresis and encopresis in children with DM1 were present in approximately 20%, a symptom with a potentially great impact on people's lives.[16] No myotonic dystrophy–targeted or myotonic dystrophy–specific treatment exists yet to treat GI manifestations, and specialty care is recommended by swallowing therapists and GI specialists.[63-65]

Ocular Symptoms in Myotonic Dystrophy Types 1 and 2

Cataracts in the posterior capsule often occur in patients with myotonic dystrophy before age 55. Cataracts were observed in 49% to 60% of patients with DM2[6,8,55] and in 12% of patients with congenital myotonic dystrophy.[16] The recent discovery of a CTG repeat expansion causing Fuchs endothelial corneal dystrophy has prompted studies on *DMPK*-mediated Fuchs endothelial corneal dystrophy.[89,90] The prevalence of Fuchs endothelial corneal dystrophy in small cohorts of patients with DM1 was 36% to 46%,[91,92] suggesting that Fuchs endothelial corneal dystrophy is a manifestation of DM1. Annual visits with an ophthalmologist are recommended.

Cancer in Myotonic Dystrophy Types 1 and 2

Several studies have shown that patients with DM1 have a greater risk of developing cancer than the general population, specifically melanoma and cancers of the thyroid, colon, and uterus,[93-95] contributing to increased mortality.[94] An association between DM1 and uveal melanoma has been recently reported.[96] Pilomatricomas are benign skin tumors that can be seen in DM1.[97,98] The mechanism underlying the increased cancer risk remains unclear,[97] but longer repeat sizes have been observed in cancer tissue. The risk of cancer in DM2 is less well studied, but data from the National Registry for Myotonic Dystrophy suggest that the risk is similar to that in DM1.[56] Currently, no evidence suggests specific cancer screening for myotonic dystrophy, but care recommendations involve adhering to age-appropriate cancer screenings according to guidelines that apply to the general population. However, providers can consider a low threshold to evaluate suspicious symptoms or lesions and consider screening for thyroid cancer with thyroid ultrasound.

Other Systemic Features in Myotonic Dystrophy Types 1 and 2

Myotonic dystrophy is associated with insulin resistance, increased cholesterol levels, and hypertriglyceridemia.[6,99,100] In a Serbian study, diabetes mellitus was present in 65% of patients with DM2.[101] Data from the National Registry for

Myotonic Dystrophy indicates that diabetes is more common in patients with DM2 compared to those with DM1.[56] Treatment with statins can exacerbate muscle symptoms and pain, and alternate medical therapies may need to be considered.

Liver function tests may reveal modest elevations of alanine, aspartate aminotransferase, γ-glutamyl transferase, and alkaline phosphatase in both DM1 and DM2; however, these do not require invasive workup if levels are stable and if no evidence exists for a comorbid disease process.

Primary hypogonadism is common in men with DM1. This may manifest with low testosterone, reduced fertility, testicular atrophy, and erectile dysfunction.[102]

IgG levels were low in 75% of patients with DM2, and 54% of patients had low lymphocyte counts.[103] The clinical significance of this is not yet established.

FUTURE PERSPECTIVE: THERAPIES TARGETING THE ROOT CAUSE OF MYOTONIC DYSTROPHY

Treatment approaches alleviating RNA toxicity include (1) reducing transcription of the toxic RNA, (2) posttranscriptional silencing of the toxic RNA, (3) releasing MBNL proteins from the nuclear foci, eg, by using small molecules to interact with (C)CUG repeat interactions, and (4) targeting signaling pathways downstream of (C)CUG repeats.[104] A CRISPR system has been used to eliminate formation of nuclear foci.[105] In mice with DM1, antisense oligonucleotide targeting *DMPK*-CUG(exp) transcripts showed a therapeutic response.[106] The first multicenter phase 1b/2b clinical trial of antisense oligonucleotide therapy in patients with DM1 (NCT02312011) showed promising effects of splicing biomarkers, but suboptimal target engagement limited the clinical effect. A phase 1/2 clinical trial is underway to evaluate short interfering RNA targeting *DMPK* mRNA conjugated with a monoclonal antibody that binds to the transferrin receptor 1 (NCT05027269). A phase 2/3 study is assessing the efficacy and safety of tideglusib in children with congenital myotonic dystrophy (NCT03692312). More clinical trials for DM1 are expected in the near future. Therapy development for DM2 is in preclinical stages and more complicated, as *CNBP* silencing may not be tolerable.

CONCLUSION

DM1 and DM2 are autosomal dominant diseases that most conspicuously affect skeletal muscle, resulting in myotonia and progressive weakness, but also variably affect other tissue types such as smooth muscle, the brain, and the heart, resulting in GI dysfunction, hypersomnolence, and cardiac conduction delays. Recognition of the diseases in clinic is important, for both genetic counseling and providing adequate care for multisystem disease manifestations. In particular, respiratory weakness and cardiac conduction delays require monitoring and management and contribute to a reduced life expectancy in DM1. Progress has been made in understanding the underlying molecular mechanism of myotonic dystrophy and treatments targeting the root cause of DM1, the toxic RNA, are being tested in clinical trials. However, the variability and diversity of the myotonic dystrophy phenotype continues to be a challenge in the clinic and in research when measuring therapeutic effects.

KEY POINTS

- Ocular manifestations of DM1 and DM2 include cataracts, often before age 55. Patients with DM1 can develop corneal dystrophy.
- The risk of developing cancer is increased in both forms of myotonic dystrophy, including melanoma and cancer of the thyroid, colon, and uterus. Age-appropriate cancer screening is recommended.
- Important metabolic and endocrinological manifestations of DM1 and DM2 include diabetes (insulin resistance), increased cholesterol, primary hypogonadism in men, and issues with fertility.
- Our understanding of the underlying mechanism in DM1 and particularly DM2 is expanding, which is a prerequisite for targeted drug development.
- To date, no therapies are available that change the trajectory of the disease, but clinical trials targeting the root cause of DM1 are currently being conducted.

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