Published in final edited form as:

JAMA. 2024 April 09; 331(14): 1227–1228. doi:10.1001/jama.2024.2511.

Diagnosis and Management of Myotonic Dystrophy Type 1

Julia Hartman, BS,
Tejal Patki, BS,
Nicholas E. Johnson, MD, Msci
Virginia Commonwealth University, Richmond

Myotonic dystrophy is an autosomal dominant form of muscular dystrophy characterized by progressive muscle weakness and wasting. Two forms of myotonic dystrophy have been described: myotonic dystrophy type 1, which affects distal muscles; and myotonic dystrophy type 2, which affects proximal muscles. Myotonic dystrophy type 1 is caused by a noncoding CTG repeat expansion within the dystrophia myotonica protein kinase (*DMPK*) gene, while myotonic dystrophy type 2 is caused by a noncoding CCTG repeat expansion within the cellular nucleic acid binding protein (*CNBP/ZNF9*) gene. RNA transcripts containing expanded CUG or CCUG repeats accumulate in the nucleus, forming foci that sequester RNA-binding proteins such as muscleblind protein (MBNL), which result in dysregulated alternative splicing, mRNA translation impairments, and mRNA instability. Patients with both types of myotonic dystrophy can present with myotonia (impaired muscle relaxation after contraction), early-onset cataracts (before age 50), or cardiac conduction abnormalities such as atrioventricular block. While symptoms may vary among individuals, myotonic dystrophy has a high penetrance rate. This article will focus on the signs and symptoms, diagnosis, and treatment of myotonic dystrophy type 1.

Myotonic dystrophy type 1 is the most common form of muscular dystrophy. A recent genetic prevalence study of 50 382 consecutive births from the New York state newborn screening program estimated prevalence to be approximately 1:2100 individuals.[1] This estimate is substantially higher than previously reported global estimates, which ranged from 5 to 20 per 100 000 individuals.[2] Additional prevalence studies are needed with representative populations in other regions of the world. In an analysis of 679 patients in a US registry, individuals with myotonic dystrophy type 1 had a 7-year delay from symptom onset to diagnosis.[3] This delay was attributed to heterogeneity of clinical findings and variable age of onset. While myotonic dystrophy type 1 most commonly presents in adulthood, it can manifest at any point in the lifespan. Patients with congenital, childhood, and classic adult-onset myotonic dystrophy type 1 are at higher risk for early mortality. A cohort study of 367 patients in Canada (participants aged 2-80 years) who were observed over a 10-year period reported a 20% mortality rate, with a mean age at death of 53.2 years. Among the 75 deaths, 43% were respiratory-related, 20% cardiovascular-related, 11% cancer-related, and 11% from sudden death.[4] Early detection of myotonic dystrophy type

Corresponding Author: Nicholas E. Johnson, MD, Msci, Virginia Commonwealth University, 1101 E Marshall St, Richmond, VA 23019 (nicholas.johnson@vcuhealth.org).

1 and effective management are important for reducing time to diagnosis, initiation of supportive care, and decreasing mortality.

Clinical Presentations of Myotonic Dystrophy Type 1

Congenital: a rare but severe form that should be suspected in neonates who present with hypotonia, clubfoot, feeding difficulties, and respiratory distress.

Childhood: symptom onset occurs in children aged 1 to 10 years, is characterized by cognitive and behavioral impairments (including autism spectrum disorder, attention deficit hyperactivity disorder, and mood disorders), and/or gastrointestinal symptoms (such as diarrhea, constipation, or fecal incontinence). These symptoms, in combination with a family history of any subtype of myotonic dystrophy type 1, should prompt clinicians to consider childhood-onset myotonic dystrophy type 1.

Adult-onset: the most common presentation, with onset after age 10 and distal muscle weakness, myotonia, and/or early-onset cataracts. The most common presenting symptoms in the registry of 679 patients with myotonic dystrophy type 1 were grip myotonia (ie, inability to quickly release a hand grip, 38%) and arm weakness (19%).[3] However, the condition can also present with cardiac conduction abnormalities, respiratory muscle weakness, and/or mild to moderate cognitive impairment.

Late-onset/mild/asymptomatic: while likely a small proportion of total cases, symptom onset occurs in patients older than 40 years of age and is characterized by mild muscle weakness, myotonia, and/or cataracts.

Diagnosis of Myotonic Dystrophy Type 1

The diagnosis is based on a patient's medical history, family history, physical examination, and genetic studies. History may reveal family history of myotonic dystrophy type 1 or personality changes (eg, avoidant behavior and/or apathy). The physical examination may reveal muscle weakness or atrophy of the neck, face, hands, and distal legs; grip myotonia or percussion myotonia (ie, tapping thenar muscles with a reflex hammer and eliciting myotonic contractions); and/or cataracts. Electromyography findings of myotonic discharges may support the diagnosis, as electrical myotonia may be present even without signs of clinical myotonia. Muscle biopsies are nonspecific and are not needed for diagnosis. The criterion standard diagnostic test is molecular genetic testing with identification of CTG repeat expansions in the *DMPK* gene. Presence of more than 34 CTG repeats is categorized as a premutation and these individuals are asymptomatic; however, the repeats can expand in future generations to pathogenic levels (ie, genetic anticipation). Individuals with 50 or more CTG repeats in the *DMPK* gene have full-penetrance alleles and typically develop clinical manifestations of myotonic dystrophy type 1. Longer CTG repeat lengths are associated with more severe symptoms and an earlier age of onset. Since myotonic dystrophy type 1 is an autosomal dominant disorder, it is important to offer genetic counseling to all first-degree relatives; they may have sudden cardiac death without other preceding symptoms.

Management and Treatment

Patients with myotonic dystrophy type 1 should have annual visits with a multidisciplinary team, composed of a primary care clinician, neuromuscular specialist, physical therapist, speech therapist, neuropsychologist, pulmonologist, cardiologist, and genetic counselor. Management recommendations for organ systems and symptoms associated with myotonic dystrophy type 1, screening tests, and recommended treatments are highlighted in the online Supplement. In-depth consensus-based care recommendations have been published for adults[5] and patients with congenital and childhood myotonic dystrophy type 1.[6]

Currently, there are no cures for myotonic dystrophy type 1; treatment focuses mainly on symptom management. For excessive daytime sleepiness, stimulants such as modafinil may be helpful. For myotonia-related symptoms(grip difficulty, swallowing and/or speech problems), mexiletine is often used and has US Food and Drug Administration orphan drug designation for myotonic dystrophy. Mexiletine enhances fast inactivation of sodium channels, counter-acting the slowed rate of fast sodium channel inactivation that leads to the repetitive firing of muscle fibers and delayed muscle relaxation characteristic of myotonia. While a phase 1/2 study with mexiletine showed individuals with myotonic dystrophy type 1 had improved grip strength, it failed to meet its primary end point of improvement in 6-minute walk distance.[7] No differences were observed on electrocardiogram between treatment groups, suggesting mexiletine was not detrimental to cardiac conduction. Phase3 trials further investigating mexiletine are underway. Regular exercise (both aerobic and strength training) has been shown to improve cardiorespiratory fitness, muscle function, and quality of life in individuals with myotonic dystrophy type 1.[8] Clinicians should encourage patients to engage in an exercise program to which they can adhere. Additionally, before prescribing medications, clinicians should consult with other members of the patient's care team, considering the potential for drug malabsorption in the gastrointestinal tract, altered drug pharmacokinetics due to changes in muscle mass, arrhythmogenicity, and potential sedating effects of medications.

A variety of medications are being investigated in clinical trials for patients with myotonic dystrophy type 1. A phase 2 randomized clinical trial reported that in 23 of 40 (57.5%) patients with myotonic dystrophy type 1 who completed the 1-year study, metformin modestly but significantly improved 6-minute walk distance by approximately 30 m compared with placebo.[9] Additionally, novel small interfering RNA and antisense oligonucleotide compounds designed to silence the mutant *DMPK* transcripts have recently entered phase 1/2 clinical trials in patients with adult myotonic dystrophy type 1.

Conclusions

Myotonic dystrophy type 1 is the most common form of muscular dystrophy and is characterized by myotonia, progressive distal muscle weakness, early-onset cataracts, and other multisystem manifestations. The diagnosis is based on a patient's medical history, family history, physical examination findings, and genetic studies; the criterion diagnostic standard is genetic testing to identify CTG repeat expansions. Treatments may focus on specific symptoms such as muscle weakness and/or atrophy, cardiac arrhythmias, fatigue,

and myotonia. Given the increasing prevalence and severity of myotonic dystrophy type 1, clinicians should be aware of the various clinical presentations and work as part of a multidisciplinary team to manage patients' symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest Disclosures:

Dr Johnson reported grants from Avidity, Dyne, Novartis, Takeda, PepGen, Sanofi Genzyme, Vertex, Fulcrum, AskBio, Sarepta, and Arthex; personal fees from Avidity, Dyne, Takeda, PepGen, Sanofi Genzyme, Vertex, Fulcrum, AskBio, Sarepta, Arthex, Juvena, Rgenta, and Design outside the submitted work; and a patent for the Congenital and Childhood Myotonic Dystrophy Health Index and for the Limb Girdle Muscular Dystrophy Health Inventory, both with royalties paid from the University of Rochester. No other disclosures were reported.

REFERENCES

1. Johnson NE, Butterfield RJ, Mayne K, et al. Population-based prevalence of myotonic dystrophy type 1 using genetic analysis of statewide blood screening program. Neurology. 2021;96(7):e1045–e1053. doi:10.1212/WNL.0000000000011425 [PubMed: 33472919]
2. Liao Q, Zhang Y, He J, Huang K. Global prevalence of myotonic dystrophy. Neuroepidemiology. 2022;56(3):163–173. doi:10.1159/000524734 [PubMed: 35483324]
3. Hilbert JE, Ashizawa T, Day JW, et al. Diagnostic odyssey of patients with myotonic dystrophy. J Neurol. 2013;260(10):2497–2504. doi:10.1007/s00415-013-6993-0 [PubMed: 23807151]
4. Mathieu J, Allard P, Potvin L, Prévost C, Bégin P. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology. 1999;52(8):1658–1662. doi:10.1212/WNL.52.8.1658 [PubMed: 10331695]
5. Ashizawa T, Gagnon C, Groh WJ, et al. Consensus-based care recommendations for adults with myotonic dystrophy type 1. Neurol Clin Pract. 2018;8(6):507–520. doi:10.1212/CPJ.0000000000000531 [PubMed: 30588381]
6. Johnson NE, Aldana EZ, Angeard N, et al. Consensus-based care recommendations for congenital and childhood-onset myotonic dystrophy type 1. Neurol Clin Pract. 2019;9(5):443–454. doi:10.1212/CPJ.0000000000000646 [PubMed: 31750030]
7. Heatwole C, Luebbe E, Rosero S, et al. Mexiletine in myotonic dystrophy type 1. Neurology. 2021;96(2):e228–e240. doi:10.1212/WNL.0000000000011002 [PubMed: 33046619]
8. Mikhail AI, Nagy PL, Manta K, et al. Aerobic exercise elicits clinical adaptations in myotonic dystrophy type 1 patients independently of pathophysiological changes. J Clin Invest. 2022;132(10):e156125. doi:10.1172/JCI156125 [PubMed: 35316212]
9. Bassez G, Audureau E, Hogrel JY, et al. Improved mobility with metformin in patients with myotonic dystrophy type 1. Brain. 2018;141(10):2855–2865. doi:10.1093/brain/awy231 [PubMed: 30169600]