Myotonic dystrophy

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Myotonic dystrophy (**dystrophia myotonica**, **myotonia atrophica**) is a chronic, slowly progressing, highly variable, inherited multisystemic disease.

It is characterized by wasting of the muscles (muscular dystrophy), cataracts, heart conduction defects, endocrine changes, and myotonia.

There are two main types of myotonic dystrophy. **Myotonic dystrophy type 1** (**DM1**), also called **Steinert disease**, has a severe congenital form and an adult-onset form. **Myotonic dystrophy type 2** (**DM2**), also called **proximal myotonic myopathy** (**PROMM**) is rarer than DM1 and generally manifests with milder signs and symptoms. Myotonic dystrophy can occur in patients of any age. Both forms of the disease display an autosomal dominant pattern of inheritance. Both "DM1" and "DM2" have Adult-Onset forms.

Myotonic dystrophy	
Classification and external resources	
ICD-10	G71.1 (http://apps.who.int/classifications/icd10/browse/2015/en#/G71.1)
OMIM	160900 (http://omim.org/entry/160900) 602668 (https://omim.org/entry/602668)
DiseasesDB	8739 (http://www.diseasesdatabase.com/ddb8739.htm)
MeSH	D009223 (https://www.nlm.nih.gov/cgi/mesh/2015/MB_cgi?field=uid&term=D009223)
GeneReviews	Myotonic Dystrophy Type 1 (http://www.ncbi.nlm.nih.gov/books/NBK1165/) Myotonic Dystrophy Type 2 (http://www.ncbi.nlm.nih.gov/books/NBK1466/)

Contents

Description/Classification

Myotonic dystrophy subtypes

Type	Gene	Repeat	Anticipation	Severity
DM1	*DMPK*	CTG	Yes	Moderate-severe
DM2	*ZNF9*	CCTG	Minimal/none	Mild-moderate

There are two main types of myotonic dystrophy. Type 1 (DM1), also known as Steinert disease, has a severe congenital form and a milder childhood-onset form as well as an adult-onset form [VALID CITATION NEEDED - Only Congenital and Adult-Onset are verifiable] . This disease in more often in the facial muscles, levator palpebrae superioris, temporalis, sternocleidomastoids, distal muscles of the forearm, hand intrinsic muscles, and ankle dorsiflexors.[1] Type 2 (DM2), also known as proximal myotonic myopathy (PROMM), is rarer and generally manifests with milder signs and symptoms than DM1.

Other forms of myotonic dystrophy not associated with DM1 or DM2 genetic mutations have been described.[2] One case which was proposed as a candidate for the "DM3" label,[3] was later characterized as an unusual form of inclusion body myopathy associated with Paget's disease and frontotemporal dementia.[2][4][5]

Myotonic dystrophy (DM) is an inherited disease, affecting males and females approximately equally. About 30,000 people in the United States are affected. Symptoms may appear at any time from infancy to adulthood. DM causes general weakness, usually beginning in the muscles of the hands, feet, neck, or face. It slowly progresses to involve other muscle groups, including the heart. DM affects a wide variety of other organ systems as well. A severe form of DM, congenital myotonic dystrophy, may appear in newborns of mothers who have DM. Congenital Myotonic Dystrophy can also be inherited via the paternal gene, although it is said to be relatively rare. Many professionals still state it is only via the maternal gene, however this has been disproved in recent years. Congenital means that the condition is present from birth. The incidence of congenital myotonic dystrophy is thought to be about 1:20,000. DM occurs in about 1 per 7,000–8,000 people and has been described in people from all over the world.

Symptoms and signs

Presentation of symptoms and signs varies considerably by form (DM1/DM2), severity and even unusual DM2 phenotypes. DM1 symptoms for DM2 include problems with executive function (e.g., organization, concentration, word-finding) and hypersomnia. Conduction abnormalities are more common in DM1 than DM2, but all patients are advised to have an annual ECG. Both types are also associated with insulin resistance. Myotonic dystrophy patients may have a cortical cataract with a blue dot appearance, or a posterior subcapsular cataract.[6]

DM2 is generally milder than DM1, with generally fewer DM2 patients requiring assistive devices than DM1 patients. In addition, the severe congenital form that affects babies in DM1 has not been found in DM2 and the early onset of symptoms is rarely noted to appear in younger patients in the medical literature.

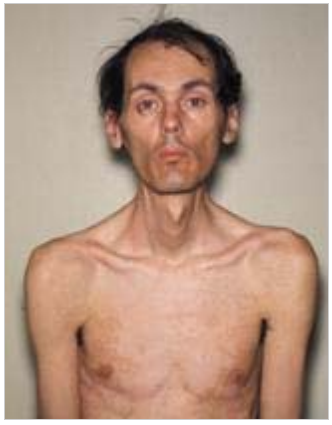
Death is unlikely but possible in both forms of myotonic dystrophy.

Genetics

Myotonic dystrophy is a genetic condition which is inherited in an autosomal dominant pattern and thus will be

passed along to 50% of a carrier's offspring, on average.

Myotonic dystrophy is one of several known trinucleotide repeat disorders. Certain areas of DNA have repeated sequences of two or three nucleotides.



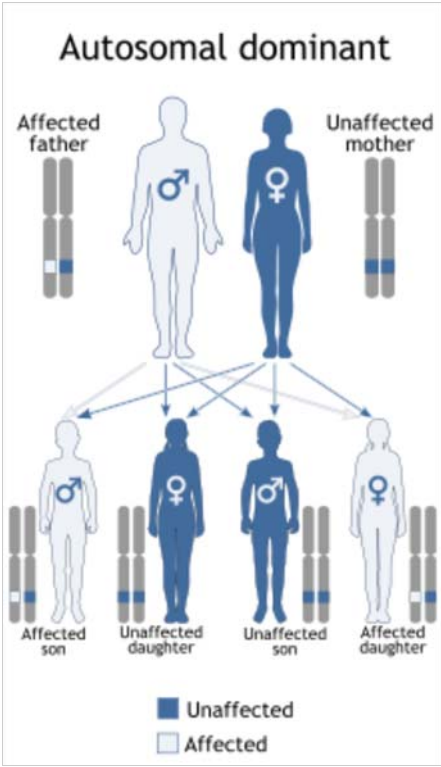
40-year-old patient with myotonic dystrophy presenting with bilateral cataracts and complete heart block.

DM1

In DM1, the affected gene is called *DMPK*, which codes for myotonic dystrophy protein kinase,[7] a protein expressed predominantly in skeletal muscle.[8] The gene is located on the long arm of chromosome 19.[9]

In DM1, there is an expansion of the cytosine-thymine-guanine (CTG) triplet repeat in the *DMPK* gene. Between 5 and 37 repeats is considered normal, while individuals with between 38 and 49 repeats are considered to have a pre-mutation and are at risk of having children with further expanded repeats and, therefore, symptomatic disease.[2] Individuals with greater than 50 repeats are almost invariably symptomatic, with some noted exceptions.[ref] Longer repeats are usually associated with earlier onset and more severe disease.

DMPK alleles with greater than 37 repeats are unstable and additional trinucleotide repeats may be inserted during cell division in mitosis and meiosis. Consequently, the children of individuals with premutations or mutations inherit DMPK alleles which are longer than their parents and therefore are more likely to be affected or display an earlier onset and greater severity of the condition, a phenomenon known as anticipation. Interestingly, paternal transmission of the condition is very uncommon, possibly due to selection pressures against sperm with expanded repeats, but anticipation tends to be less severe than in cases of maternal inheritance.



Myotonic dystrophy is inherited in an autosomal dominant pattern.

DM2

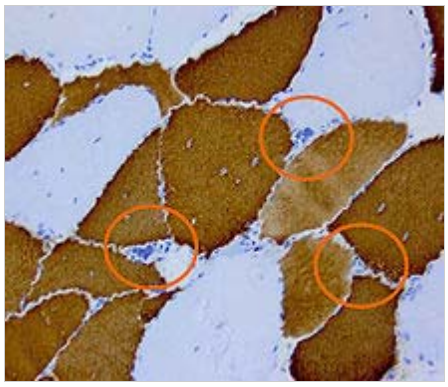
DM2 is caused by a defect of the *ZNF9* gene on chromosome 3.[10] The specific defect is a repeat of the cytosine-cytosine-thymine-guanosine (CCTG) tetranucleotide in the *ZNF9* gene.[10] As it involves the repeat of four nucleotides, it is not a trinucleotide repeat disorder, but rather a tetranucleotide repeat disorder.[11]

The repeat expansion for DM2 is much larger than for DM1, ranging from 75 to over 11,000 repeats.[10] Unlike in DM1, the size of the repeated DNA expansion in DM2 does not appear to make a difference in the age of onset or disease severity.[2] Anticipation appears to be less significant in DM2 and most current reviews only report mild anticipation as a feature of DM2.

Diagnosis

The diagnosis of DM1 and DM2 can be difficult due to the large number of neuromuscular disorders, most of which are very rare. More than 40 neuromuscular disorders exist with close to 100 variants.

As a result, patients with multiple symptoms that may be explained by a complex disorder such as DM1 or DM2 will generally be referred by their primary care physician to a neurologist for diagnosis. Depending on the presentation of symptoms, patients may be referred to a number of medical specialists including cardiologists, ophthalmologists, endocrinologists, and rheumatologists. In addition, the clinical presentation is obscured by the degree of severity or the presence of unusual phenotypes.



Histopathology of DM2. Muscle biopsy showing mild myopathic changes and grouping of atrophic fast fibres (type 2, highlighted). Immunohistochemical staining for type-1 ("slow") myosin

It is common that the clinical presentation for both DM1 and DM2 patients does not conform to the perceptions of these diseases held by many neurologists. Clinicians who are less familiar with the myotonic dystrophies in their day to day practice may expect patients with both forms to present with the more severe classic symptoms of DM1. As a result, patients may remain undiagnosed or be misdiagnosed. A useful clinical clue for diagnosis is the failure of spontaneous letting go of the hands following strong handshakes due to myotonia (delayed relaxation of muscles after contraction) which accompanies muscle weakness.

Even though there is presently no cure for DM and management is currently symptom based, a precise diagnosis is still necessary because of multiple other problems that may develop over time (e.g. cataracts). An accurate diagnosis is important to assist with appropriate medical monitoring and medical management of symptoms. In addition, genetic counseling should be made available to all patients because of the high risk of transmission. Potentially serious anesthetic risks are important to note, so the presence of this disorder should be brought to the attention of all medical providers.

Prenatal testing

Genetic tests, including prenatal testing, are available for both confirmed forms. Molecular testing is considered the gold standard of diagnosis.

Testing at pregnancy to determine whether an unborn child is affected is possible if genetic testing in a family has identified a DMPK mutation. This can be done at 10–12 weeks gestation by a procedure called chorionic villus sampling (CVS) that involves removing a tiny piece of the placenta and analyzing DNA from its cells. It can also be done by amniocentesis after 14 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it and those who are interested in learning more should check with their doctor or genetic counselor. There is also another procedure called preimplantation diagnosis that allows a couple to have a child that is unaffected with the genetic condition in their family. This procedure is experimental and not widely available. Those interested in learning more about this procedure should check with their doctor or genetic counselor.

Predictive testing

It is possible to test someone who is at risk for developing DM1 before they are showing symptoms to see whether they inherited an expanded trinucleotide repeat. This is called predictive testing. Predictive testing cannot determine the age of onset that someone will begin to have symptoms, or the course of the disease.

Management

There is currently no cure for or treatment specific to myotonic dystrophy. Therefore, the focus is on managing the complications of the disease, particularly those relating to the cardiopulmonary system as these account for 70% of deaths due to DM1.[2] Pacemaker insertion may be required for individuals with cardiac conduction abnormalities. Central sleep apnoea or obstructive sleep apnoea may cause excessive daytime sleepiness, and these individuals should undergo a sleep study. Non-invasive ventilation may be offered if there is an abnormality. Otherwise, there is evidence for the use of modafinil as a central nervous system stimulant, although a Cochrane review has described the evidence thus far as inconclusive.

Some small studies have suggested that imipramine, clomipramine and taurine may be useful in the treatment of myotonia.[2] However, due to the weak evidence and potential side effects such as cardiac arrhythmias, these treatments are rarely used.

Altered splicing of the muscle-specific chloride channel 1 (ClC-1) has been shown to cause the myotonic phenotype of DM1 and is reversible in mouse models using Morpholino antisense to modify splicing of ClC-1 mRNA.[12]

Physical Therapy interventions

Physical activity

Combined strengthening and aerobic training at moderate intensity was deemed safe for individuals with neuromuscular diseases[13] and the combination was found to increase muscle strength.[14] Specifically, aerobic exercise via stationary bicycle with an ergometer was found to be safe and effective in improving fitness in DM1 patients.[15] The strength training or aerobic exercise may promote muscle and cardiorespiratory function, while preventing further disuse atrophy.[13] Cardiovascular impairments and myotonic sensitivities to exercise and temperature necessitate close monitoring of patients and educating patients in self-monitoring during exercise via the Borg scale, heart rate monitors, and other physical exertion measurements.[16]

Orthotics

Muscular weakness of dorsiflexors (dorsiflexion) hinders the ability to clear the floor during the swing phase of gait and patients may adopt a steppage gait pattern[16] or ankle-foot-orthotics may be indicated.[2] Factors such as hand function, skin integrity, and comfort must be assessed prior to prescription. Neck braces can also be prescribed for neck muscle weakness.[2]

Mobility aids and adaptive equipment

Upper and lower limb weakness, visual impairments and myotonia may lead to the need for mobility aids and functional adaptive equipment such as buttonhooks and handled sponges for optimal hand function. If assistive devices and home adaptations are needed, physical therapists may refer on to occupational therapist(s) for further assessment.[2]

Epidemiology

DM1 is the most common form of myotonic muscular dystrophy diagnosed in children, with a prevalence ranging from 1 per 100,000 in Japan to 3-15 per 100,000 in Europe.[2] The prevalence may be as high as 1 in 500 in regions such as Quebec, possibly due to the founder effect. In most populations, DM1 appears to be more common than DM2. However, recent studies suggest that type 2 may be as common as type 1 among people in

Germany and Finland.[17]

Research

The years since the discovery of the genetic cause of MMD in 1992 have been fruitful ones for MMD research. Scientists are gaining understanding of how the expanded DNA section on chromosome 19 causes so many physiologic changes. In the meantime, scientists are also working to test drug treatments that may help symptoms in MMD. Among these are a drug that can make muscles more sensitive to insulin, one that may help improve muscle function and one that may relieve myotonia. The ultimate ―cure for MMD would probably require finding a way to block the expanded area of DNA on chromosome 19 or chromosome 3 so that it would lose its toxic effect on cells. It is not far-fetched to imagine that, in the future, this expanded section of DNA could be blocked or ―silenced. Scientists around the world are studying the unusual biological mechanisms that underlie MMD and working on pathways to treatment. However, it needs to be understood that such a treatment will take many years to be sufficiently developed to be used on humans.

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External links

- National Registry for Myotonic Dystrophy (http://www.urmc.rochester.edu/neurology/national-registry/)
- *Myotonic dystrophy (http://ghr.nlm.nih.gov/condition=myotonicdystrophy)* at NLM Genetics Home Reference
- GeneReview/NCBI/NIH/UW entry on Myotonic Dystrophy Type 1 (http://www.ncbi.nlm.nih.gov/books/NBK1165/)
- GeneReview/NCBI/NIH/UW entry on Myotonic Dystrophy Type 2 (http://www.ncbi.nlm.nih.gov/books/NBK1466/)
- Searchable database (http://www.isno.nl/sorteer/ziekten.php) at Dutch Neuromuscular Research
- Udd B, Meola G, Krahe R, et al. (June 2006). "140th ENMC International Workshop: Myotonic Dystrophy DM2/PROMM and other myotonic dystrophies with guidelines on management" (http://linkinghub.elsevier.com/retrieve/pii/S0960-8966(06)00097-6). *Neuromuscul. Disord.* **16** (6): 403–13. doi:10.1016/j.nmd.2006.03.010 (https://dx.doi.org/10.1016%2Fj.nmd.2006.03.010). PMID 16684600 (https://www.ncbi.nlm.nih.gov/pubmed/16684600). Myotonic Dystrophy DM2/PROMM and other Myotonic dystrophies]
- Information (http://www.myotonic.org/medical-information/about-the-disorder/) from the Myotonic Dystrophy Foundation
- Information (http://www.myotonicdystrophy.org) from the International Myotonic Dystrophy Organization (IMDO)
- MDSG Information (http://www.myotonicdystrophysupportgroup.org/)
- Information (http://www.DMCanada.org) from Myotonic Dystrophy Canada (DMCanada)
- Information (http://www.neuro.wustl.edu/neuromuscular/index.html) from the Neuromuscular Disease Center
- DM Toolbox (http://www.marigoldfoundation.org/dmtoolbox.htm) Research tools for Myotonic Dystrophy from the Marigold Foundation
- Facts about myotonic muscular dystrophy (http://www.mda.org/publications/PDFs/FA-MMD.pdf) from Myotonic Dystrophy Association

Categories: Autosomal dominant disorders | Muscular dystrophy | Myoneural junction and neuromuscular diseases | Trinucleotide repeat disorders