PAPER

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Myotonic dystrophy

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ABSTRACT Myotonic dystrophy is the most common form of muscular dystrophy in adults, with a prevalence of 1 in 8,000. It is a slowly progressive, multi-system disorder that affects skeletal muscles, the heart, gastrointestinal smooth muscle, uterine smooth muscle, the eyes, and the endocrine and central nervous systems. Myotonic dystrophy is almost always caused by an autosomal dominant gene mutation in the *DMPK* gene located on chromosome 19. The gene mutation is an expansion in the length of a three base-pair (triplet) repeat sequence (cytosine–thymine–guanine, or CTG) above the normal upper limit of 35 repeats. The expanded CTG repeat is classed as a 'dynamic' mutation because the number of repeats tends to increase in size over successive generations in myotonic dystrophy families. In general, larger CTG expansions are associated with earlier age-of-onset and more severe signs and symptoms of myotonic dystrophy. Patients with 50–100 CTG repeats may develop cataract, diabetes, grip myotonia, or mild muscle weakness in mid to late adulthood. Patients with 200–500 CTG repeats are affected earlier and more severely by facial and distal limb muscle weakness and myotonia. A CTG repeat size above 1,000 is associated with prenatal onset of disease and congenital myotonic dystrophy, which may be fatal due to respiratory failure. Feeding difficulties, muscle weakness, club foot deformity, and cognitive impairments are present in surviving infants. Although males and females are equally likely to inherit myotonic dystrophy, the very large mutations (>1,000 repeats) which result in the congenital form of myotonic dystrophy are virtually always transmitted by an affected mother. DNA tests are used to estimate repeat size and permit accurate prenatal, presymptomatic, and diagnostic genetic testing.

LIST OF ABBREVIATIONS Central nervous system (CNS), cytosine–thymine–guanine (CTG), electrocardiogram (ECG), messenger RNA (mRNA), myotonic dystrophy protein kinase (DMPK), myotonic dystrophy type 1 (DM1), myotonic dystrophy type 2 (DM2), zinc finger transcription factor 9 (ZNF9)

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INTRODUCTION

Myotonic dystrophy type 1 is a progressive, inherited muscular dystrophy with an estimated prevalence of 1 in 8,000. It is unlike other muscular dystrophies because it is a multi-system disorder that presents in a large variety of ways (see Table 1). The age of onset of symptoms ranges from before birth to old age, but can be considered under three main categories. Classical myotonic dystrophy patients have muscle weakness, myotonia, and a range of other symptoms, in early to mid adult life; congenital myotonic dystrophy patients have severe symptoms at birth; mildly affected adults may have weakness, myotonia, cataract, or diabetes in mid to late adulthood. Although there are other rare genetic types of myotonic dystrophy, this article deals specifically with DM1.

GENETICS

Myotonic dystrophy type 1 is one of a group of neurogenetic conditions termed 'triplet repeat disorders'. It is caused by an expansion in the size of a three base-pair (triplet) repeat sequence in the *DMPK* gene. The repeat, comprising CTG, occurs up to 35 times in unaffected individuals. In patients with myotonic dystrophy, the number of repeats is greater than 50. As the number of repeats increase, signs and symptoms become more prominent, with earlier age of onset. In general, patients with 50–100 repeats are mildly affected; those with 200–500 repeats are classically affected; and those with more than 1,000 repeats have congenital or childhood-onset disease. However, in an individual patient, the repeat size is a poor predictor of clinical prognosis.

TABLE I Presentations of myotonic dystrophy.

Specialty	Presenting scenario
Obstetrician	Polyhydramnios, premature delivery.
Neonatologist	Neonatal respiratory distress, hypotonia, weakness, feeding difficulties, club foot deformity.
Paediatrician	Muscle weakness, hypotonia, drooling, 'clumsiness', mild learning difficulties, speech problems, dysphagia, abdominal pain, diarrhoea, constipation, soiling.
Adult Physician	Muscle weakness, myotonia, diabetes, cardiac conduction defect/arrhythymia, dysphagia, diarrhoea, constipation, abdominal pain, respiratory infections.
Neurologist	Muscle weakness, myotonia.
Gynaecologist/ Urologist	Subfertility, impotence.
Orthodontist/ Craniofacial surgeon	Temporomandibular joint pain, jaw malocclusion.
Intensive Care Specialist	Post-operative respiratory failure.
Ophthalmologist	Early onset bilateral, posterior subcapsular cataract.
Clinical Geneticist	Diagnosis of congenital myotonic dystrophy leads to examination of relatives.
General Practitioner	Any of the above, note that symptoms can overlap with 'myalgic encephalomyelitis'.

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Myotonic dystrophy is an autosomal dominant condition. When one parent carries the mutation, there is a 50% chance that it will be transmitted to his or her child. Males and females are equally likely to be affected. However, the clinical severity tends to increase in successive generations in a family, a phenomenon termed 'anticipation'. This is due to the dynamic nature of the repeat expansion, which tends to increase in size as it is passed from parent to child. The largest expansions are only transmitted in the egg cell, so the most severe manifestation, congenital myotonic dystrophy, is virtually always transmitted by an affected mother.

PATHOGENESIS

The CTG repeat mutation is located towards the end of the *DMPK* gene and its corresponding mRNA, but is outwith the part of the mRNA that is translated into protein. Many of the effects of the mutation result from effects of the abnormal, expanded mRNA, which binds to different nuclear proteins that, in turn, affect the processing of other genes. Changes affecting insulin receptor mRNA and muscle chloride channel mRNA cause insulin resistance and myotonia, respectively. The repeat expansion also leads to reduction in the level of DMPK protein itself, and this affects ion channels, altering the excitability

FIGURE 1 Moderately affected myotonic dystrophy patient. Note ptosis and facial muscle weakness.

of skeletal and cardiac muscle. The repeat expansion affects the amount of protein made from adjacent genes, and reduced levels of one of these, SIX5, is implicated in the pathogenesis of cataract in myotonic dystrophy.

CLINICAL FEATURES OF MYOTONIC DYSTROPHY

Classically affected adults

These patients have facial weakness, ptosis, hollowing of the temples due to temporalis muscle wasting, atrophy of the jaw muscles (see Figure 1), and, particularly in males, early frontal balding. Dysarthric, hypernasal speech is prominent. Grip myotonia is often the first symptom. Percussion myotonia is elicited in the thenar and tongue muscles but the latter is painful for patients. Muscle weakness and wasting affect the sternocleidomastoids and distal limb muscles first, whilst proximal limb musculature is affected later. Weakness is slowly progressive, but the rate of progression and each individual's prognosis is difficult to predict. Even in the late stages of the disease, most patients retain at least limited mobility.

Non-neuromuscular symptoms of myotonic dystrophy can be disabling and challenging to manage (see Table 2). Daytime hypersomnolence is common and does not correlate with the severity of muscle involvement. Central nervous system mechanisms are thought to underlie most cases and modafinil is helpful in some. Hypersomnolence can also be a symptom of nocturnal hypoventilation, and in these patients nocturnal non-invasive ventilation improves symptoms.

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TABLE 2 Common clinical features of myotonic dystrophy and their management.

Symptom/Sign	Management
Muscle weakness	Occupational therapy; physiotherapy; orthotics.
Myotonia	Heated gloves; anti-myotonic medication rarely required.
Temporomandibular joint dysfunction	Physiotherapy.
Cardiac conduction abnormalities, arrhythmias	Consider 24-hour ECG at diagnosis; annual ECG; 24-hour ECG if increasing PR interval or other risk arrhythmia.*
Dysphagia	Speech therapy; behavioural modifications (neck flexed when swallowing).
Gastrointestinal symptoms	Various treatments according to cause, specialist gastroenterology assessment recommended.
Ptosis	Consider surgery if affects vision, but rarely required.
Cataract (posterior subcapsular)	Annual eye assessment.
Blepharitis	Lubricant eye drops.
Diabetes	Annual glucose measurement.
Testicular atrophy	Testosterone unhelpful.
Male subfertility	Assisted conception (intracytoplasmic sperm injection).
Impotence	
Daytime hypersomnolence	Modafinil helps some cases; exclude respiratory involvement.
Respiratory failure	Respiratory assessment; nocturnal non-invasive ventilation; offer influenza and Pneumococcus vaccination.
Raised liver enzymes	Awareness can avoid unnecessary investigation.
Gallstones	

*Recommendation of the European Neuromuscular Centre workshop on cardiac management of myotonic dystrophy.

Gastrointestinal symptoms arise from delayed gastric emptying, smooth muscle and sphincter dysfunction, bile acid malabsorption, and small bowel bacterial overgrowth. Cholestyramine improves diarrhoea, incontinence, and pain in some patients, and metoclopramide is helpful for symptoms related to delayed gastric emptying. In difficult cases, referral to a gastroenterologist is recommended.

Endocrine complications of myotonic dystrophy include diabetes mellitus, which is increased approximately fourfold. Testicular atrophy, with degeneration of the seminiferous tubules, results in reduced spermatogenesis and subfertility in some males.

Respiratory complications account for 30–40% of deaths in myotonic dystrophy. Reduced central drive and respiratory muscle weakness contribute to nocturnal hypoventilation. This results in difficulty wakening, feeling unrefreshed after sleep, morning nausea and headaches, reduced energy levels, and daytime somnolence. Non-invasive nocturnal ventilation improves symptoms and may prolong survival, but the myotonic dystrophy patient's compliance with this treatment is often poor; this may reflect reduced drive and reduced ability to sustain interest in activities, which are common CNS complications of myotonic dystrophy.

Cardiac involvement is frequent and sudden cardiac death occurs in 10–30% of patients. The severity of cardiac complications does not correlate with the degree of muscle weakness or the size of the repeat expansion. Approximately 65% of adults have an abnormal electrocardiograph. Conduction abnormalities (atrioventricular more commonly than intraventricular) and arrhythmias (atrial more commonly than ventricular) predominate, whereas cardiomyopathy is rare. Pacemakers are required in 5% of patients but their insertion does not prevent sudden death due to ventricular arrhythmia. The optimal intensity of cardiac surveillance and the role of 24-hour ECG monitoring is disputed, but a European Neuromuscular Centre workshop has considered cardiac management of myotonic dystrophy and published evidence-based guidelines.

Myotonic dystrophy patients are at increased risk of complications of general anaesthesia, such as hypotension, pulmonary aspiration, and respiratory depression. Risks are maximal in undiagnosed patients for whom post-operative respiratory failure is a serious hazard. Elective surgery requires detailed pre-operative cardio-respiratory assessment and careful intra- and post-operative monitoring. Drugs that are arrhythmogenic, that precipitate myotonia, or depress respiration (such as

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FIGURE 2 Congenitally affected child with mother. Note open-mouthed appearance of child and subtly reduced facial expression in mildly affected mother.

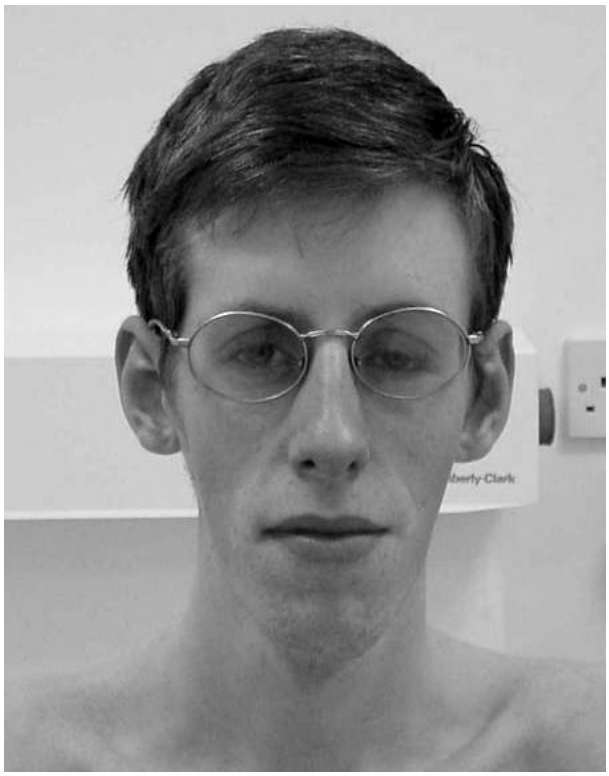

FIGURE 3 Patient with childhood-onset myotonic dystrophy. Note ptosis and facial weakness.

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depolarising neuromuscular blocking agents) should be avoided. Local or regional anaesthetic alternatives should be considered.

Pregnancy and delivery risks in females with myotonic dystrophy result from involvement of uterine smooth muscle. When the fetus is severely affected, impaired fetal swallowing and movement also contribute. There is an increased risk of placenta praevia, polyhydramnios, preterm birth, and postpartum haemorrhage. Specialist obstetric care is required but, not infrequently, the affected mother is only diagnosed after the birth of her affected infant.

Usually, the management of myotonic dystrophy patients and their extended families is coordinated by the general practitioner, neurologist, or clinical geneticist. An 'Alert' card, or patient-held care card, is useful to inform health care professionals about complications of myotonic dystrophy. The Myotonic Dystrophy Support Group and the Muscular Dystrophy Campaign are sources of support and information for patients, and the latter group fund care advisors to provide family support.

Mildly affected adults

These patients may be diagnosed only after genetic studies in their family, or may present with isolated cataract or diabetes. Mild weakness of grip or myotonia in late adulthood is often overlooked by the patient. Cardiac complications still occur in this group and cardiac surveillance is required.

CONGENITAL AND CHILDHOOD-ONSET MYOTONIC DYSTROPHY

Pregnancies that result in the birth of a congenitally affected child are frequently complicated by polyhydramnios and premature birth. At birth, infants are hypotonic and weak, and often require mechanical ventilation and nasogastric tube feeding owing to respiratory failure and reduced ability to suck or swallow. Club foot deformity also occurs in most infants.

In older studies, high mortality rates, ranging from 17–41%, were due to respiratory muscle weakness and complications of prematurity. However, with improved neonatal intensive care, survival has improved. Feeding and respiratory problems also improve with age. In older infants, facial weakness results in a characteristic open-mouthed appearance (see Figure 2), and drooling can be problematic. Cardiomyopathy has occurred in a small number of infants and an echocardiogram at diagnosis is recommended. Interestingly, myotonia is not present in the first decade.

Most children have mild learning difficulties. Virtually all children learn to walk, although this may be delayed, partly related to the surgery and/or orthotic intervention that is required for foot deformity. As in adults, gastrointestinal symptoms can be prominent.

Childhood-onset myotonic dystrophy is defined by onset of symptoms after one year and is intermediate in severity

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between congenital and adult myotonic dystrophy (see Figure 3). In congenital and childhood-onset cases, myotonia and distal limb muscle weakness develop during the teenage years. Although ECG abnormalities are common, sudden cardiac death is rare before the mid-teenage years. Unlike congenital myotonic dystrophy, childhood-onset disease is found in the offspring of affected males as well as females.

GENETIC COUNSELLING IN MYOTONIC DYSTROPHY

The smallest expansions of 50 to 60 repeats are found in older, unaffected, or mildly affected individuals, who are in topmost generations of the family tree. Such small repeat expansions are unstable during gamete production and the repeat size rises when the mutation is transmitted to the next generation.

Usually, several relatives of each affected patient are themselves at risk of having inherited the disorder. Relatives who have symptoms can be offered a DNA-based diagnostic test, but asymptomatic individuals should be offered referral to the genetic clinic to discuss the genetic implications of their family history, and options such as DNA-based presymptomatic or prenatal testing. For females with myotonic dystrophy, the chance that an infant who inherits the mutation has congenital disease (as opposed to childhood or later onset disease) is much higher if the mother is symptomatic than if she is asymptomatic. Interestingly, when females already have a congenitally affected child, subsequent children inheriting the mutation are always congenitally affected.

Genetic testing of children requires special consideration. Symptomatic children are assessed by a paediatrician or neurologist and diagnostic testing may follow. Genetic testing of the asymptomatic child is not recommended: there are no obvious treatment benefits, medical complications are unlikely, and routine testing in childhood removes the right of the informed adult to choose not to be tested. Anxious parents sometimes request testing of their healthy children but after detailed discussion at the genetic clinic, it is usually possible for this to be postponed until the child is mature and can make an informed decision.

For couples who wish to avoid the birth of an affected infant but who are unable to contemplate medical termination of an affected pregnancy, *in vitro* fertilisation techniques and pre-implantation genetic diagnosis is one option that has recently become available in a few specialist centres.

OTHER FORMS OF MYOTONIC DYSTROPHY: PROXIMAL MYOTONIC MYOPATHY (DM2)

Fewer than 5% of patients with myotonic dystrophy have a different condition that shows considerable clinical overlap with DM1. Myotonic dystrophy type 2 (previously called proximal myotonic myopathy, PROMM) is due to a tetranucleotide (CCTG) repeat expansion in the *ZNF9* gene located on chromosome 3. A congenital form has not been described in DM2, and perhaps very large expansions in the *DM2* gene have a lethal effect on the fetus. Family studies also indicate the existence of at least one other myotonic dystrophy gene.

KEYPOINTS

- Myotonic dystrophy is a multisystem disorder that displays marked variability in signs and symptoms: the non-neuromuscular complications of myotonic dystrophy may be severely disabling or fatal.
- Myotonic dystrophy is caused by an autosomal dominant gene mutation. Each affected person, male or female, has a 50% chance of transmitting the disease gene to their child.
- Cardiac arrhythmias and conduction defects are common and their severity does not correlate with the severity of muscle involvement or the size of the gene mutation. Regular cardiac monitoring is required.
- In myotonic dystrophy families, there tends to be progressively younger age of onset of disease with increasing clinical severity in successive generations. Congenital myotonic dystrophy is nearly always transmitted by an affected mother.
- Patients are at increased risk of anaesthetic complications, and should carry a 'MedicAlert' or similar card.

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FURTHER READING

- Harper PS, van-Engelen B, Eymard B, Wilcox DE (editors). *Myotonic dystrophy. Present management and future therapy.* (1st ed.) Oxford: Oxford University Press; 2004.
- Harper PS. *Myotonic dystrophy.* (3rd ed.) London: WB Saunders; 2001.
- Machuca-Tzili L, Brook D, Hilton-Jones D. Clinical and molecular aspects of the myotonic dystrophies: A review. *Muscle Nerve* 2005; **32(1):**1–18.
- Day JW, Ranum LP. RNA pathogenesis of the myotonic dystrophies. *Neuromuscul Disord* 2005; **15(1):**5–16.
- Bushby K, Muntoni F, Bourke JP. 107th ENMC international workshop: the management of cardiac involvement in muscular dystrophy and myotonic dystrophy. 7th–9th June 2002, Naarden, the Netherlands. *Neuromuscul Disord* 2003; **13(2):**166–72.