

Muscular Dystrophy Ireland Myotonic Dystrophy Information Day Report

Muscular Dystrophy Ireland held the first ever information day for people with myotonic dystrophy in Ireland on Saturday 26th September 2009. Out of a membership of 529 as of September 2009, MDI has 73 members registered as having myotonic dystrophy, which is the third highest diagnosis after Duchenne muscular dystrophy and the condition Charcot-Marie-Tooth. The following is a report on the day.

**Jacqueline Turner
Genetic Counsellor, NCMG, Crumlin**

The National Centre for Medical Genetics (NCMG) is composed of three specialist departments:

- Clinical Genetics Department
 - 4 Consultant Clinical Geneticists
 - 6 Genetic Counsellors (2 part-time)
 - Secretarial support
- Cytogenetics Department
- Molecular Genetics Department

The Clinical Genetics Department sees families and individuals who have or potentially have a genetic condition. The service is free and funded by the Department of Health. Self referrals to the service are not accepted unless the family is already known to the NCMG, but any medical professional can make a referral for you. It is a national service. Although it is based in Crumlin Hospital, there are also clinics held in Galway, Letterkenny, Cork and Limerick.



Karen Pickering, MDI Information Officer with Jacqueline Turner

The American Society of Human Genetics defined genetic counselling as a communication process which deals with human problems associated with the occurrence of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to:

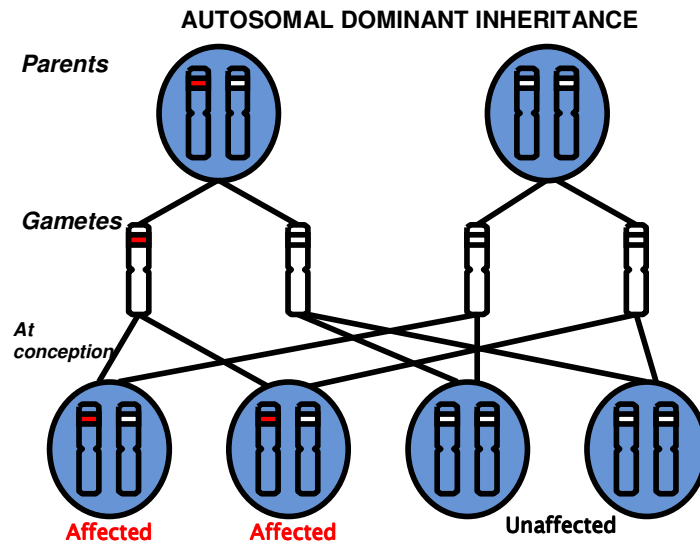
- Comprehend the medical facts, including diagnosis, probably course of the condition and available management.
- Appreciate the way hereditary factors contribute to the condition and risk of recurrence in specified relatives.
- Understand the alternatives for dealing with the risk of recurrence.
- Choose a course of action which seems appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision.
- To make the best possible adjustment to the condition in an affected family member and / or to minimise the risk of recurrence of that condition.

Myotonic dystrophy (DM) was first described by Steinert in Germany in 1909. In 1982, the gene was mapped to chromosome 19 and in 1992, the genetic alteration that causes DM was shown to be an unstable CTG repeat. The estimated incidence of DM varies according to different studies but Harper's estimation in 1989 of 1 in 20,000 is mostly accepted.

DM is also a multisystem disorder, affecting skeletal as well as smooth muscle, the eye, heart, endocrine and central nervous systems. The main characteristics are muscle weakness, myotonia (stiffness), cardiomyopathy and cardiac conduction abnormalities and cataracts. As the condition progresses, muscle weakness becomes the predominant problem including swallowing difficulties, followed by respiratory and cardiac problems. Cataracts are common later in the condition.

Roughly two thirds of people with DM have an abnormal electrocardiogram. They may not have any symptoms but some might present with blackouts. Heart checks are therefore essential for people with DM.

Regarding diagnosis, most people come to medical attention for minor symptoms or following the birth of a child with severe congenital myotonic dystrophy. While onset is typically in the 20s – 30s, it can occur in childhood and infancy and less commonly after 40. It is an autosomal dominant condition, meaning that it is inherited from one parent who has the condition. New mutations are rare, most people have a family history of the condition. Some people with DM might not be aware of a family history but when it is examined, they find that other relatives do have it but they were asymptomatic or had mild symptoms which did not lead to a diagnosis before.



In the diagram above, it shows that children inherit two copies of each chromosome, one from each parent. A chromosome is made up of different genes. As we have two of each chromosome, we have two copies of each gene. A person with DM has two copies of chromosome 19, one with the gene change that causes DM (the red band above) and one that would work fine if the altered gene wasn't present (the white band above). Every time a person with DM has a child, that child has a 50% chance of inheriting the altered gene and having DM, and a 50% chance of being completely unaffected.

It has still not been determined exactly how the altered gene causes the muscle weakness or other clinical problems associated with DM. The gene for DM makes a protein kinase called DMPK. However, this abnormal protein is not associated with disease. The unstable triplet repeat in the DMPK gene (called a CTG repeat) is in an area of the gene not used to make the protein. It is possible that the RNA that is produced interferes with the cellular processing of RNA produced by other genes, or the CTG expansion influences expression of not only the protein kinase but of other genes close by.

Myotonic dystrophy can be classified according to severity – mild, classic and congenital – and this generally correlates with the size of the CTG repeat (the repeat length can be different in different tissues though).

Normal	5-34 CTG repeats
Premutation	>34-49 repeats
Mild	50~150
Classic	~150~1000
Congenital	>2000

The diagram below demonstrates the clinical forms of DM:

		Age of diagnosis	Inheritance
Premutation	No symptoms		May transmit a larger gene to children
Mild	Cataracts Mild Myotonia Diabetes	20-70 years	AD; Anticipation
Classic	Muscle weakness Myotonia Cardiomyopathy Cataracts Frontal hair loss	10-30 years	AD; Anticipation
Congenital	Symptoms discussed in another slide	Birth-10 years	

In the congenital form of DM, the child has almost always inherited the gene change from the mother, unlike other forms which can be inherited from the mother or father. Mortality from respiratory failure is high in congenital DM, however, children who survive gradually improve in motor function. The rate of non-progressive intellectual disability is high however (50-60%).

The risk of having a child with the congenital form of DM generally depends on the repeat length of the mother. With a CTG of less than 300 in the mother, the risk of having a child with the congenital form is 10%. With a CTG repeat of over 300 in the mother, this rises to a risk of 59%. These are estimated risks as they depend on the repeat lengths in the mother's gonads.

Myotonic dystrophy tends to show earlier onset and increasing severity with successive generations, and the repeat length increases with successive generations.

The management of DM includes:

- Two yearly eye examination: cataracts can be detected by slit-lamp examination in the early stages of the condition and cataracts can be removed if vision is impaired.
- People with DM should have an annual cardiac assessment because of the high risk of electrocardiogram abnormality.
- Annual measurement of fasting serum glucose concentration and treatment for diabetes mellitus if needed.
- People with DM can be sensitive to relaxants and sedation so anaesthetics can be a risk. Anaesthetists should be aware of the condition and careful monitoring post operatively is necessary.

There are potential complications for pregnancy in a woman with DM, including an increased miscarriage rate, prolonged labour, premature delivery and risk of a child born with the congenital form. Prenatal testing is possible. The condition needs to be confirmed molecularly in the parent and then CVS and amniocentesis are possible for prenatal testing. It can predict the presence of the condition but it cannot predict the age of onset or the severity of the symptoms, although CTG repeats of 730-1000 are more likely to be associated with congenital DM. Preimplantation genetic diagnosis (PGD) is available in the UK and Belgium. It is essentially an IVF procedure, where fertilized eggs are tested and only those that are unaffected are transplanted into the uterus.

If anyone would like to be seen by the National Centre for Medical Genetics, ask a medical professional to make a referral for you if your family has not been seen before. If the family have been seen before, ring the Department, stating who was seen.

Dr. Ronan Walsh, Consultant Neurologist



Dr. Walsh giving his talk

The most common myotonic disorder is myotonic dystrophy type 1 (DM1). Less commonly, there are myotonic dystrophy type 2 (DM2), myotonia congenital, paramyotonia congenital, potassium aggravated myotonias, hyperkalemic periodic paralysis and drug induced myotonia (cholesterol lowering agents (statins and fibrates), cyclosporine and chloroquine).

DM1 is the most prevalent inherited neuromuscular condition in adults. The prevalence in the west is around 13.5 per 100,000 live births. The ratio of males to females is 1:1. It may present at any age but earlier onset and a more severe condition is associated with longer CTG repeats.

Myotonia means that there is a slow relaxation of muscles after voluntary contraction so generally, repeated effort is needed to relax the muscles.

People might notice that they have trouble releasing their grip on objects. They may also have difficulty rising from a sitting position and a stiff, awkward gait. Symptoms of myotonia are more frequent in pregnancy.

Myotonic dystrophy weakness tends to be in these areas:

- Cranial
 - Face: eye and mouth closure, temporal muscle
 - Ptosis, i.e. drooping eyelids
 - Palate and tongue: indistinct speech
- Neck: head drop
- Proximal
 - Quadriceps (thigh): difficulty going up stairs
 - Diaphragm and intercostals: breathless
 - Affected later in the condition
- Distal
 - Hand grip
 - Foot drop

There are also features of myotonic dystrophy in the endocrine system. These can include reduced testosterone, reduced release of growth hormone and insulin resistance. This is important to watch out for as it causes diabetes.

Systemic manifestations of myotonic dystrophy include effects on the heart, breathing and gastro-intestinal tract. Cardiomyopathy can occur as well as conduction defects and arrhythmias. An ECG should be carried out every 6-12 months and if an arrhythmia is suspected, an EPS (electrophysiology study) can be carried out. Respiratory symptoms can include sleep apnoea or pulmonary hypertension.

In order to diagnose DM1, an EMG can show signs of myotonia. CK levels which are elevated in some conditions such as Duchenne are usually normal in myotonic dystrophy. A muscle biopsy can show ring fibres but DNA testing for CTG or CCTG repeats will give a definitive diagnosis.

There are various ways in which the symptoms of myotonic dystrophy can be managed. The myotonia itself often doesn't need treatment but if it does, mexiletine or phenytoin can be used. Excessive sleepiness might indicate further examination to look for obstructive sleep apnoea. Modafanil can sometimes be used for daytime sleepiness. When it comes to cardiac management, there should be an annual ECG. A holter monitor to record the heart's rhythms can be used if there is evidence of risk of bradycardia (slow heart beat). Atrial tachyarrhythmias (atrial flutter, fibrillation) can require antiarrhythmia treatment. Treatment with a pacemaker is indicated when a progressive arrhythmia is detected even prior to symptoms.

A person with myotonic dystrophy should make an anaesthetist aware of their condition before any surgery as there can be a risk from general anaesthesia and neuromuscular blocking agents. Genetic counselling is very important. In people affected by them, cataract excision may be performed.

The multidisciplinary approach is very important in myotonic dystrophy:

- Regular neurology review
- Regular cardiology review
- Regular respiratory review
- Physiotherapy
- Occupational therapy
- Dietician

In myotonic dystrophy type 2 (DM2), people tend to have more pain and discomfort from myotonia leading to more management of this symptom. DM2 is rare in Ireland although it is more common in Germany.

There are potential future treatments of myotonic dystrophy being looked at although these are in the early stages of research. One potential avenue of exploration is induced over-expression of something called Muscleblind (MBNL1) to counteract the toxic effect of RNA accumulation.

Prof. Richard Costello, Consultant Respiratory Physician



Margaret Goode, MDI Family Support / Clinic Coordinator, Prof. Costello and Joe Mooney, CEO of MDI

Prof. Costello hosted a question and answer session regarding respiratory issues. Sleep is important for different functions such as retaining memories. Sleep length varies between different individuals, some need more than others. However, there is a difference between the quantity and quality of sleep. Prof. Costello spoke of the difference between tiredness and sleepiness. You need to know if your muscles are tired because they are weak or are you sleepy due to insufficient sleep or poor sleep quality as arises from conditions like sleep apnoea. Snoring or falling asleep at inappropriate times can indicate sleep apnoea but a sleep study is needed to confirm this diagnosis.

Sleep apnoea leads to poorer quality sleep. Sleeping on your side will not stop sleep apnoea and it is not due to weakness in the muscles – the respiratory muscles not working properly can lead to respiratory failure which can happen in the later stages of the condition and is managed in a different way.

To manage sleep apnoea, a C-PAP machine can be used. This uses continuous pressure to blow the airway open. When the problem is that the diaphragm is weak, a Bi-PAP can be used. This blows air in and then the pressure is turned off to allow you to breathe out. Some people with myotonic dystrophy find the masks that are need with these machines quite uncomfortable, however others have a better experience.

Excessive daytime sleepiness can also be treated with modafanil / provigil.

There is a group of people with myotonic dystrophy whose immunoglobulin runs low and this can lead to recurrent ear / sinus / chest infections. If people have these recurrent infections and experience excessive sleepiness, they should see a respiratory specialist. People with myotonic dystrophy can have a weak cough and it is recommended to have a cough bottle on standby to help keep the airway open when necessary. A useful cough bottle could be exputex, casacol or alupent. An antibiotic is also useful to have at home in case of a chest infection developing.

Margaret Bowler, Myotonic Dystrophy Support Group UK

Margaret's husband and son were both diagnosed with myotonic dystrophy at the same time. After this they wanted to meet other people with the same condition so over time the group formed. It has grown over the years and they now have 1600 people on their mailing list. They provide a lot of information which is all free, so they just ask for a £10 subscription to cover some of the costs. One of the things that they produce is an alert card because of the potential risk from general anaesthetic. This means that if someone needs emergency surgery and cannot explain that they have myotonic dystrophy, the alert card will make medical professionals aware.



Margaret Bowler addressing the audience

Elycia Ormandy, Myotonic Dystrophy Support Group UK

Elycia spoke about the IDM7 meeting which recently took place in Germany. It is a scientific meeting but patient groups are asked to attend as they add focus to the researchers' work. Great excitement, encouragement and hope came from the meeting. Researchers are now collaborating internationally and are working toward clinical trial readiness. There is now a need for an international registry of people with myotonic dystrophy to prepare for trials starting up. Although there are no myotonic dystrophy clinical trials taking place yet, they will come.



Elycia Ormandy