Centronuclear and myotubular myopathy

What are centronuclear and myotubular myopathies?

The centronuclear myopathies are a group of rare inherited neuromuscular conditions that cause muscle weakness and hypotonia (lack of muscle tone). The symptoms range from severely disabling conditions that are diagnosed at birth to relatively mild ones with onset in adulthood.

There are three forms: X-linked, autosomal recessive and autosomal dominant. These classifications are based on the way in which the conditions are passed down through families (see “how are centronuclear myopathies inherited” below). X-linked centronuclear myopathy is also known as myotubular myopathy.

The word ‘myopathy’ comes from the Greek word ‘myo’ meaning muscle and the word ‘pathy’ which means disease. The ‘centronuclear’ part of the name refers to the appearance of the muscle when looked at under a microscope. Usually muscle fibres have their nucleus (control centre) located at the edge but in people with centronuclear myopathy the nucleus is in the centre of the muscle fibre.

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What are the symptoms and what is the prognosis?

**Myotubular myopathy (X-linked centronuclear myopathy)**

This is the most common of the centronuclear myopathies affecting approximately 1 in 50,000 new-born boys worldwide. It is also the most severe form with muscle weakness and hypotonia (lack of muscle tone) noticeable at birth. It only affects males (with rare exceptions). The muscle weakness can cause life-threatening difficulties with feeding and breathing and a feeding tube and assisted ventilation are usually needed. Some individuals need breathing assistance only periodically, typically during sleep, while others require it continuously. Because of the severe breathing difficulties many babies with this condition die in early infancy whereas others survive into childhood. A few people with this condition have lived into adulthood.

The development of motor skills such as sitting, standing, and walking are impaired in children with myotubular myopathy. Intellectual ability (cognitive function) is not thought to be affected. Language skills might be delayed if the child has a tracheostomy (a tube is inserted into the neck to help them breathe) but a speaking valve can help with this.

Contractures (joints frozen in place because of muscle weakness) may develop, particularly in the hips and knees. Spinal curvature (scoliosis) also may develop in childhood. The muscles of the face may be weak including those that control eye movement. Myotubular myopathy is generally considered a non-
progressive or slowly progressive condition.

There are also incidences of women who are carriers of the gene that causes myotubular myopathy having muscle weakness. These women are referred to as “manifesting carriers”.

**Autosomal recessive centronuclear myopathy**

The autosomal recessive (AR) form of centronuclear myopathy causes progressive muscle weakness, is less severe than myotubular myopathy and affects both males and females. Symptoms are usually present at birth or appear in early childhood. Weakness of the muscles in the face may occur, especially the muscles used for chewing. The muscles around the eyes are often weak and the eyelids may also droop (ptosis). Some people may have problems with feeding and breathing which ranges from mild to severe, but in general most patients do not need to use a ventilator full-time.

Other symptoms of AR centronuclear myopathy may include foot abnormalities, a high-arched palate, curvature of the spine (scoliosis) and urinary incontinence. Very rarely the heart muscle is weakened (cardiomyopathy).

The severity of AR centronuclear myopathy is widely variable. Those people without severe breathing or heart problems generally have mild, slowly progressing muscle weakness and have a good prognosis.

**Autosomal dominant centronuclear myopathy**

Autosomal dominant (AD) centronuclear myopathy is generally the mildest type of centronuclear myopathy and men and women with this condition don't start to experience muscle weakness until adolescence or early adulthood. The age of onset is widely variable and the first symptoms are usually difficulty walking and sometimes muscle pain during exercise. People with this condition may have weakness in the muscles that control eye movement (ophthalmoplegia) and droopy eyelids (ptosis). Muscle weakness progresses slowly with AD centronuclear myopathy and most don’t need a wheelchair until they are in their sixties.

However, some children with autosomal dominant centronuclear myopathy are more severely affected and experience muscle weakness in infancy. These individuals walk at a later age than their peers, and they typically need wheelchair assistance in childhood or adolescence.

**What causes centronuclear myopathies?**

Centronuclear myopathies are genetic conditions caused by the presence of a mistake in the DNA (which is often referred to as a ‘mutation’). These DNA errors are within genes that are responsible for the production of proteins that are important for muscle function. The protein is then either not produced or doesn’t work properly.

Changes to the DNA code of several genes have been found to cause centronuclear myopathies. X-linked myotubular myopathy is caused by changes to the myotubularin (MTM1) gene only whereas AD centronuclear myopathy is known to be caused by changes to the dynamin 2 (DNM2) and ryanodine receptor 1 (RYR1). Genes involved in AR centronuclear myopathy include bridging integrator 1 (BIN1) (also known as amphiphysin 2), ryanodine receptor 1 (RYR1) and titin (TTN).

How these gene mutations cause the muscle weakness is not well understood but it is thought that myotubulin is a protein that promotes normal muscle development and maintenance. When this protein is absent or inactive, the muscles don’t form properly. Dynamin 2 is part of the transportation system for substances inside cells and is also part of the cell’s structural framework. The ryanodine receptor is involved in muscle contraction and amphiphysin 2 protein is involved in the maintenance of the membrane surrounding muscle fibres. Titin is an essential component of structures within muscle cells called sarcomeres, which are the basic units of muscle contraction.

Some people are found not to have changes to any of these genes and so the cause is unknown. Research is ongoing to find more genes causing centronuclear myopathy so that these people can gain a genetic diagnosis.
How are centronuclear myopathies inherited?

Myotubular myopathy (X-linked centronuclear myopathy)
Myotubular myopathy is ‘X-linked’, meaning that the myotubularin gene that causes it is situated on the X chromosome. Females have two X chromosomes one inherited from each parent. In most cases females who inherit a faulty myotubularin gene will show no symptoms of the disorder. This is because the healthy gene on her other X chromosome will be predominant and function to produce myotubularin. Women with the faulty myotubularin gene on one of their X-chromosomes are known as carriers and can pass the condition onto her children.

Males have one X chromosome which they inherit from their mother and one Y chromosome which they inherit from their father. If a boy’s mother is a carrier of a faulty myotubularin gene there is a 50:50 chance that he will inherit this gene and will have myotubular myopathy because, unlike females, he doesn’t have another X chromosome to make up for the faulty one.

The daughters of carriers each have a 50:50 chance of being carriers. Occasionally female carriers have a mild degree of muscle weakness, and these women are known as ‘manifesting carriers’.

Autosomal recessive centronuclear myopathy
For an individual to have AR centronuclear myopathy, they need to inherit two altered genes - one from their mother and one from their father. The genes (see “what causes centronuclear myopathies” above) are located on the autosomal chromosomes, that is, the chromosomes other than the X and Y sex-determining chromosomes. This is what is called an ‘autosomal recessive’ inheritance pattern.

The parents of an individual with AR centronuclear myopathy each carry one copy of the altered gene, and are known as ‘carriers’, but they typically do not show signs and symptoms of the condition. Their other ‘good’ copy of the gene is enough to prevent the condition. In order for carrier parents to have a child affected by AR centronuclear myopathy, both parents must pass the altered gene on to their child. If both parents are carriers the likelihood of a child inheriting the condition is 25 percent, or 1 in 4.

Autosomal dominant centronuclear myopathy
The inheritance of one altered copy of the gene (see “what causes centronuclear myopathies” above) from either parent is sufficient for a person to be affected by an autosomal dominant disorder. The single altered gene is sufficient to over-ride the normal functioning copy inherited from the other parent. Each affected person usually has one affected parent. The chance of a child inheriting the condition from a parent with the condition is 50 percent, or 1 in 2.

How is centronuclear myopathy diagnosed?
If a doctor suspects that a child or adult might have centronuclear myopathy the first step to gaining a diagnosis is usually a muscle biopsy. This is a minor surgical procedure, which involves removing a small piece of muscle for analysis. There are two types of muscle biopsy; open and needle, and these are both usually conducted under a local anaesthetic but may be performed under a general anaesthetic. The muscle sample is sent to a laboratory where it is examined under a microscope. Results are usually available in a few weeks.

Muscle MRI (magnetic resonance imaging), a type of non-invasive body imaging is also sometimes used to narrow down the diagnosis. This scan shows the pattern of muscle wasting throughout the body which can indicate certain types of myopathy. Finally the DNA is analysed to confirm the diagnosis (please see “what causes centronuclear myopathies below”). Such a genetic test can determine precisely which gene is altered. For rare conditions such as these, genetic testing can be a long and complicated process and take some time for a result to be available. For some people it is not possible to find the genetic mutation causing the condition, but as research advances a precise genetic diagnosis may be possible in the future.

Why is genetic counselling important?
Soon after the diagnosis of centronuclear myopathy it is essential that genetic counselling is arranged, together with appropriate tests for those members of the family who are at risk of being carriers. Genetic
counselling provides information on the inheritance pattern, risks to other family members, and the ‘prognosis’ (likely outcome of the disorder). Family members who are found to be carriers of the condition can discuss with a genetic counsellor family planning options to reduce the risk of passing the condition on to future children.

**How can the symptoms be managed?**

No curative treatment is currently available for any form of centronuclear myopathy but management by a multidisciplinary team of doctors can do a lot to manage the symptoms and improve quality and length of life.

For babies with X-linked myotubular myopathy intensive, continuous support of feeding and ventilation can significantly improve life expectancy and allow good quality of life. Babies born with severe autosomal recessive or dominant centronuclear myopathy may also require intensive support with breathing and feeding but these children have been known to improve over time.

Close monitoring of breathing function is required for those not on a ventilator. When the respiratory muscles weaken, air doesn’t move into and out of the lungs very well, with subsequent adverse effects on general health. Signs of weakening respiratory muscles are headaches, difficulty sleeping at night, excess sleepiness during the day, poor concentration and chest infections. Portable, effective ventilation devices are available which can greatly improve quality of life. These are often only needed at night.

Respiratory infections should be promptly treated and a speech therapist can help manage swallowing difficulties and promote normal speech development. Monitoring by a cardiologist may also be recommended in some cases, because although heart defects are not usually a feature of centronuclear myopathy, breathing difficulties can have a negative effect on the heart function.

Regular physiotherapy can help preserve muscle power and function and prevent contractures. Exercise such as swimming and bike riding which promote endurance and core stability may also be particularly useful. Orthopaedic complications such as scoliosis and contractures may need surgery in some cases. As in other neuromuscular conditions, patients should not stay immobile in bed for a long time after surgery or during illness as this may result in muscles wasting away quickly.

A cautious approach is generally advisable for patients with muscle disorders going for general anaesthesia. This is especially true for those with a mutation in the ryanodine receptor gene (RYR1). These people are susceptible to malignant hyperthermia - an abnormal, life threatening response to muscle relaxants. As a precaution those without a genetic diagnosis should also be wary of this potential complication.

Palliative care should be sought to proactively prepare patients and their families for the long-term consequences of their condition and engage in discussions regarding end-of-life care if applicable. For those with myotubular myopathy and severe centronuclear myopathy the decision regarding the duration of respiratory support is not an easy one, but as the course of the disease is very variable from patient to patient, this decision should be made on an individual basis by the family.

More information about managing the symptoms of centronuclear myopathy, especially in regards to respiratory management can be found in the links in “Further information” and “References” below.

**What research is being done?**

Much of the research into centronuclear myopathies is focused on understanding how the gene mutations cause the symptoms of the condition and discovering new gene mutations. This work is essential before a therapy can be developed. In addition, a lot of progress has been made in recent years towards developing potential therapies; especially for myotubular myopathy since the gene causing this condition has been
known and studied for many years.

Animal models that accurately mimic centronuclear myopathy are vital tools for research and the development of treatments. Researchers have now developed yeast, worm, fish, fruit fly, mouse and dog models of myotubular and/or centronuclear myopathy. Although these animals might seem a long way removed from humans, they are very useful for scientists to study and understand how molecules are interacting within the cells and test potential therapies.

One of the promising treatments being researched in France and the USA for X-linked myotubular myopathy is gene therapy. The aim of gene therapy is to introduce a healthy synthetic copy of a gene into the body to compensate for the one that is faulty. A harmless virus is used to deliver the gene into the cells of the body where these instructions are used to make the missing protein. In this case, the myotubularin gene was delivered to the muscles of mouse and dog models of myotubular myopathy using a virus called AAV (adeno-associated virus). The animals lived longer and had improved muscle function. This proves that this could be a viable way to treat children with myotubular myopathy but more work is required before a clinical trial can proceed. Encouraging news was announced in February 2014 - US-based biotechnology company Audentes Therapeutics entered into a partnership with French research organisation Genethon to develop AAV gene therapy for myotubular myopathy.

In 2013 another research group in Boston USA published results of research that involved directly replacing the missing myotubularin protein in a mouse model of myotubular myopathy. After two weeks of treatment, the mice showed improvement in muscle function. Researchers are continuing to study this potential therapy to determine if it appears to be safe and non-toxic and what dose would be required to treat children before a clinical trial can be planned.

In March 2014, researchers in France reported on another potential way to treat centronuclear and myotubular myopathy. This relates to the discovery that two of the genes causing these conditions appear to work together in the same biological process. They found that the myotubularin protein (which is lacking in children with X-linked myotubular myopathy) is normally an inhibitor of dynamin 2. Myotubular myopathy therefore leads to increased levels of dynamin 2 protein in the muscles. Previous studies have also shown that the mutations in the dynamin 2 gene that cause centronuclear myopathy, rather than decreasing the amount of dynamin 2 protein, actually lead to increased activity of the protein. So it appears that increased activity of dynamin 2 is bad for the muscles. The researchers then reduced levels of dynamin 2 in mice that are a model of myotubular myopathy and found that these mice had much improved muscle function and a normal life span. So the researchers are now searching for drugs suitable for use in humans that inhibit dynamin 2.

Studying animal models of the different types of centronuclear myopathy has revealed that the muscles have some features in common with another muscle condition called “congenital myasthenic syndrome” (CMS). In this condition there is a problem with the transmission of signals from the nerves to the muscles to tell them to contract. This prompted researchers to test some of the drugs that are used to treat CMS on mouse models of centronuclear myopathy and the results were positive. A few patients have tried these medications, mostly because they were initially misdiagnosed with CMS, and improvements in strength have been reported. However it isn’t clear yet which patients might benefit so further investigations are being done before recommendations are made about prescribing these drugs.

Before any clinical trials can start for conditions as rare and varied as the centronuclear myopathies, groundwork needs to be done to understand and locate patients worldwide. For this purpose there is the Myotubular and Centronuclear Myopathy Patient Registry. This database collects information about people with myotubular and centronuclear myopathies for the purpose of raising awareness, improving standards of care and encouraging and facilitating research and clinical trials. People with the condition or their family members can register through the registry website. Women who are carriers of x-linked myotubular myopathy are also invited to join the registry.
NOTE: Research is moving forward at a fast pace, so this research summary may not be up-to-date at the time of reading. Feel free to contact MDA’s Scientific Communications Officer for an update on the latest developments - kristina.elvidge@mda.org.au.

Further information

- UK charities “The Information Point for Centronuclear and Myotubular Myopathy,” and the “Myotubular Trust” and “The Joshua Frase Foundation” in the USA are good sources of information and support for families.
- Information about centronuclear and myotubular myopathy on the TREAT-NMD website
- Download the “Guidelines for Respiratory Management of Children with Neuromuscular Weakness”
- Download the leaflet “Guidance on breathing and non-invasive ventilation (NIV) for children from the age of two years old living with a neuromuscular condition”
- Clinical trials – your questions answered
- More information about patient registries
- Download the “Family Guide to Myotubular Myopathy” which is published by the Joshua Frase Foundation
- You can get regular updates by becoming a friend of the MDA Facebook page or follow our Scientific Communications Officer on Twitter (@kelvidge).

For further information on any of the areas discussed above, please contact MDA on (03) 9320 9555, email info@mda.org.au

References


Glossary

**Gene**: Genes are made of DNA and each carries instructions for the production of a specific protein. Genes usually come in pairs, one inherited from each parent. They are passed on from one generation to the next, and are the basic units of inheritance. Any alterations in genes (mutations) can cause inherited disorders.

**Mutation**: A permanent change in the DNA code that makes up a gene. Depending on where the mutation occurs, and the type of mutation, they can either have no effect or result in genetic diseases such as muscular dystrophy. Mutations can be passed on from generation to generation.

**Protein**: Proteins are large molecules composed of one or more chains of building blocks called ‘amino acids’ in a specific order. The order is determined by the gene that contains the instructions for the construction of the protein. Proteins are required for the structure, function, and regulation of the body’s cells, tissues, and organs. They are the building blocks of our bodies. We have millions of different proteins in our body and each has unique functions. Two examples are the enzymes in our stomach that digests our food and the collagen which holds our skin together.
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Revised and uploaded April 2014