Overview
Centronuclear myopathies fall under the umbrella of the congenital myopathies. They are characterized by muscle weakness, and are generally apparent from birth (‘congenital’ means ‘from birth’).

They get their name from the appearance of the muscle biopsies under the microscope. The nuclei are situated in the centre of the muscle fibres, rather than on the outer edges. Centrally-located nuclei are a common feature of immature muscle but not of healthy, mature muscle.

There are several different types of centronuclear myopathy (CNM), described according to the pattern of inheritance seen (see below). Each of these is very rare. There is currently no effective treatment or cure for these myopathies, so management of the conditions is very important. It can include physiotherapy, and where necessary, the use of ventilation and/or a feeding tube.

Symptoms
Symptoms of myotubular and centronuclear myopathies, although thought to be non-progressive, may change with time, especially as the child grows. The needs of individuals with the condition may change over time.

CNM is a non-progressive, or slowly progressive, condition. For babies born with XLMTM, however, the condition may progress rapidly into respiratory failure leaving most needing respiratory support for at least some hours of the day or night. The autosomal forms are usually less severe, with few notable exceptions.

X-linked myotubular myopathy (or XLMTM)
This is the most severe form of centronuclear myopathy. It usually affects only males, and has the earliest onset. Often, but not always, there are signs of the condition before the baby is born.
These can include reduced foetal movement and often an excessive accumulation of amniotic fluid around the baby. Most individuals with XLMTM are born with severe floppiness (hypotonia) and muscle weakness. Infants may fail to breathe spontaneously at birth and most will require breathing support. There are usually problems with feeding, in particular swallowing, and persistent breathing problems. Chest infections may occur frequently because of a weak or non-existent cough function.

A child with XLMTM may appear to have a long face, and it can seem expressionless. Their eyelids may be puffy, and some of the muscles in the eyes may not work well, so they are unable to move or close their eyelids fully. There may also be tightening (contractures) of the knee and ankle joints.

The severity of the condition varies considerably among individuals. Some may not survive the first few months of life, and those who do may show improvement in the first few years, and then may become severely disabled. Many will require ventilation to support their breathing. Occasionally, some improve significantly and experience only mild weakness even into adulthood. For those requiring breathing support from birth or early in life, this is unlikely.

**Autosomal dominant CNM**

Onset of this form is variable, ranging from birth to adulthood. It usually presents later than in other forms of CNM and generally, it is not as severe as XLMTM. The condition usually follows a mild course. There is weakness in the muscles closest to the trunk of the body, although some may experience weakness in other muscles. It is important to monitor heart and lung function, although involvement of these organs is rare.

**Autosomal recessive CNM**

With onset occurring in infancy or early childhood, this form can vary considerably in severity: from XLMTM-like, to later onset and milder variants. Weakness of the muscles in the face can be common, as can droopiness of the eyelids and limitation of eye movements. Some may have problems with feeding and/or breathing, occasionally requiring a feeding tube and/or breathing support. There is usually weakness of the muscles closest to the trunk of the body (known as axial and proximal muscles).

A number of different genes are associated with this form of CNM, with mutations in the RYR1 gene being the most common cause. Individuals with mutations in the TTN gene can often have curvature of the spine (scoliosis) and/or stiffness of the spine (rigid spine). Cardiac disease (cardiomyopathy) can affect people with mutations in the TTN or SPEG10 genes. Cardiac monitoring is therefore recommended in individuals affected by these specific forms of centronuclear myopathy.

**Causes**

There are different types of CNM, which are defined by the gene affected and the pattern of inheritance seen (please see our inheritance factsheet for more information). There are also sporadic cases where there is no previous family history, but the prevalence of these has not yet been determined.
X-linked CNM (myotubular myopathy)

Thought to be the most common form of centronuclear myopathy, myotubular myopathy (XLMTM) is caused by a mutation in the myotubularin (MTM1) gene, which produces a protein called myotubularin. This protein, which is lacking in patients with XLMTM, is required in muscle development for the formation of adult muscle and for muscle maintenance.

Myotubular myopathy gets its name from the appearance of the muscle biopsies under the microscope. They show the presence of structures that look like 'myotubes' or immature muscle cells.

The MTM1 gene is located on the X chromosome. All individuals have 46 chromosomes, two of which are the sex chromosomes. Females have two copies of the X chromosome, while males have one copy of X and one copy of the Y chromosome. If a male's X chromosome has the MTM1 mutation, he will have the condition.

If a female has the mutation on one of her X chromosomes, usually her other X chromosome will compensate and she will not have the condition. She will, however, be a carrier of the condition and could pass the mutated X chromosome on to her children. It is also possible for female carriers to have symptoms of XLMTM (known as ‘manifesting carriers’), although this is quite rare.

Autosomal dominant CNM

Our genes are inherited in pairs, with one copy coming from each parent. ‘Autosomal dominant inheritance’ means that a mutation on one copy of the gene will cause the condition. The other, healthy copy cannot compensate. This form of CNM is rare and affects both males and females, often in different generations within the same family.

A large proportion of cases of autosomal dominant CNM result from mutations in the dynamin 2 (DNM2) gene. Alterations in DNM2 have also been implicated in two different neuromuscular conditions where the peripheral nerves are affected. These are called dominant intermediate Charcot Marie Tooth neuropathy (CMT) and CMT type 2M.

Autosomal recessive CNM

‘Autosomal recessive inheritance’ means that two copies of the mutated gene are needed to cause the condition. In other words, each parent carries a copy of the mutated gene. In contrast to autosomal dominant inheritance, however, the parents don’t usually show any signs of the condition. This form of the condition is rare and affects both males and females.

Several genes are known to be associated with autosomal recessive forms of CNM. This includes the BIN1 gene, encoding a protein called amphiphysin 2, and the RYR1 gene, encoding a protein called ryanodine receptor 1. Mutations in the RYR1 gene have also been implicated in other congenital myopathies, namely central core disease (CCD), multi-minicore disease (MmD) and congenital fibre type disproportion (CFTD).

Recently, recessive forms of centronuclear myopathy have also been attributed to mutations in the TTN gene, which is implicated in several other congenital myopathies but also cardiac muscle
Another rare form associated with cardiac involvement is due to mutations of the SPEG10 gene. As genetic research moves forward, it is likely that other genes responsible for centronuclear myopathies are going to be identified.

**Diagnosis**

Clinical signs and symptoms are usually the first indication of problems with the muscles. These signs are often not specific, so a muscle biopsy is required to support the potential diagnosis of CNM and to differentiate it from other types of myopathy. Genetic testing and identification of a mutation in a disease gene will then confirm the diagnosis.

**Muscle Biopsy**

Muscle biopsies are done in one of two ways:

- an open biopsy, where a small piece of muscle is taken under a general anaesthetic, or
- a needle biopsy to remove a small muscle sample with a special needle through a small incision. This requires a local anaesthetic

The samples will then be analysed under a microscope. The appearance of muscle from people with myotubular myopathy is similar to that seen in foetal muscle. The nuclei are centrally located (‘centronuclear’), instead of being at the outer edges of the muscle fibres (see figure 1 below). Our muscle biopsies factsheet will give you more information.

The pink circles are muscle fibres and the dark purple spots are the nuclei of the muscle fibres. The white arrows highlight the difference between healthy muscle (top) and muscle affected by CNM (bottom). You’ll see in the healthy muscle, the nuclei are on the outer edges of the muscle fibres. In
muscle affected by CNM (bottom), you’ll see some of the nuclei are in the centre of the muscle fibres.

Genetic Testing

This is currently available as a diagnostic service for some of the genes in autosomal recessive CNM. It is likely that more genes will be identified in future. Genetic testing involves taking a blood sample and analysing the DNA for the presence of a mutation (or alteration). This process can take a few weeks up to several months to complete, depending on the size of the gene. Analysis of the TTN gene in particular can be challenging, as this is the biggest gene we have. Sometimes further investigations are needed to clarify the mutation that is responsible for the condition. Once the gene mutation has been identified in the affected person, it is possible to test other family members who might be carriers.

Treatment

There is currently no cure or effective treatment for any forms of CNM. Active management of the condition is very important. Some principal guidelines have been outlined for the congenital myopathies, which you can find out more about below.

Ventilation

Breathing problems are common in people with CNM, and it is not unusual for a baby or child with XLMTM to require long-term breathing support for at least some hours of the day and/or night. A decrease in oxygen intake can lead to, among other things, headaches, breathlessness, poor appetite and disturbed sleep.

Regular monitoring of respiratory function is important, even in those who appear to be more mildly affected. If a respiratory problem is identified, the muscles that control breathing can be supported with a bi-pap ventilator, which is a small portable machine that assists with breathing. It can be used with or without supplementary oxygen.

Some people who require a lot of breathing support in the day and night may need ‘invasive’ ventilation. This means placing a tracheostomy tube into the windpipe through a small incision. For those who do not require continuous breathing support, ‘non-invasive’ ventilation – involving the use of a face or nose mask – may be a better option. Discuss both options fully with a consultant to determine which is more appropriate for the individual.

Feeding tube (or gastrostomy)

This is a tube that goes into the stomach through the stomach wall, through which food and fluids can pass directly. People with a myopathy may have problems swallowing, and this can lead to choking and inhalation of food. It can also lead to chest infections. A feeding tube prevents all this from happening. There are a number of different types of feeding tube available, and they are fitted by a short surgical procedure. Read our gastrostomy factsheet for more information.
Physiotherapy

This can help to maintain breathing capacity, delay the onset of curvature of the spine (scoliosis), and prevent the permanent tightening of muscles and joints (contractures). It can also assist in increasing or maintaining function and mobility. It is important that the physiotherapist involved be familiar with the treatment of people with myopathies. Respiratory physiotherapy in the form of ‘airways clearance’ is also an important aspect of the day-to-day management of life with a congenital myopathy, especially if this requires a ventilator for at least some of the day.

Exercise

There is some debate over whether people with congenital myopathies should undertake strenuous physical exercise. Some say that putting additional strain on already weakened muscles will cause additional harm, while others believe exercise may increase muscle strength. There is insufficient evidence to support either view, but moderate, non-weight bearing exercises such as swimming, walking or horse-riding may be the best solution. This sort of aerobic exercise helps to maintain a healthy cardiovascular system and a steady weight. It is, however, important to discuss this fully with your GP and consultant.

Antibiotics

Chest infections are common in those with XLMTM and some forms of autosomal CNM, and complications with breathing can lead to a variety of other problems, including lethargy, headaches, and poor appetite. There is a variety of antibiotics available to treat chest infections, and your GP can advise on the most suitable. If there is a tendency to get chest infections, it is worth considering vaccines against pneumococcal disease and the flu.

Cardiac monitoring

This is recommended for people with mutations in the TTN or SPEG10 genes, as their heart muscle may be weakened.

Other things to consider

Anaesthetics

It has now been recognised that the use of general anaesthetics can cause a number of different problems in people with muscle-wasting conditions. Although anaesthetics are generally well-tolerated by most people with myotubular and centronuclear myopathies, there are some potential issues that can cause problems with breathing. Generally, if you’re properly assessed and monitored, the risks associated with anaesthetic use are low. It’s vital that the medical
professionals involved, particularly the anaesthetist, are fully aware that you or your child has a form of myopathy.

However for people with mutations in the RYR1 gene, there is a risk of malignant hyperthermia (MH), an adverse reaction to certain general anaesthetics and muscle relaxants. For this reason, caution is advised when administering general anaesthetics to people with RYR1-related CNM.

Always ensure whoever is handling your care is aware of your condition so you can receive treatment that is most appropriate to you. Read our anesthetics factsheet for more information.

Medical alert card

This is one way to ensure health professionals are aware of your condition, should you require treatment. Many companies are able to provide a Medic Alert Card, which you can wear or carry, and which contain essential medical information. For your information, speak to your consultant.

Care plans

MDUK can provide you with a care plan so you can keep track of the medical professionals who handle your care, and any specific health needs you may have. Get in touch with us to request one.

Family planning

To find out about planning a family when you have a muscle-wasting condition, read our genetic counselling and family planning factsheets. We recommend that couples discuss this with their GP, who can then make a referral to a local clinical geneticist or genetic counsellor.

Research and clinical trials

If you’re interested in taking part in research and clinical trials, we’d recommend signing up to the Myotubular and Centronuclear Myopathy Patient Registry.

Patient registries are databases that contain information about individuals affected by a particular condition. With permission, researchers can access this information and recruit eligible patients to clinical studies. Registries also can also help clinicians to develop care standards and give patients a link to the research community. The MTM/CNM Registry sends out bi-annual newsletters to keep its participants updated on research, clinical trials and any other relevant information and events.

The MTM/CNM Registry is jointly funded by Muscular Dystrophy UK and the Myotubular Trust. For further information about centronuclear and myotubular myopathy and ongoing research, please visit the Myotubular Trust website.

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If you have feedback about this factsheet or want to request references, please email info@musculardystrophyuk.org.

**Here for you**

The friendly staff in the care and support team at the Muscular Dystrophy UK’s London office are available on 0800 652 6352 or info@musculardystrophyuk.org.

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