Muscular Dystrophy New Zealand

What is Congenital Muscular Dystrophy?

Congenital muscular dystrophy (CMD) refers to a group of muscular dystrophies that become apparent at or near birth. Muscular dystrophies in general are genetic, degenerative diseases primarily affecting voluntary muscles. CMD is rare (affecting about 1 in 50,000 babies) and both males and females are equally likely to have this condition. CMD causes muscle weakness early in life - within the first six months of birth. The first symptoms are poor head control and weak muscles, which make the baby seem floppy. There may be stiff joints (contractures) due to the baby not being able to move the joints enough.

There are different types of CMD, which vary from person to person in how severe they are, and in whether or not they get worse (progress). In many cases, CMD is not progressive, so that although the child continues to have difficulties, their muscle strength improves with time, and the child should have a normal lifespan. Some types of CMD are more severe or progressive. In these cases, the muscle weakness is more pronounced, and the child may have other problems such as seizures, learning difficulties, breathing problems. The more severe types of CMD have a poorer outlook. Extensive and ongoing research in the area of muscular dystrophies is promising, however there is currently no known cure for CMD. Intervention is directed towards helping CMD patients to enjoy the quality of life that others may take for granted.

Voluntary muscle (skeletal, striped or striated muscle). Muscle that is under control of the will and is generally attached to the skeleton. This does not include heart muscles.

Contractures are muscles or tendons that have remained too tight for too long, thus becoming shorter. Once they occur they cannot be stretched or exercised away.

With the discovery of defects in several genes in the last two decades, the concept of CMD has evolved from a narrowly defined clinical diagnosis (onset in the first months of life) and histologic diagnosis (dystrophic muscle on biopsy) to a more inclusive group of subtypes defined by the specific genes in which these defects occur. However no complete or satisfactory classification system exists. To make things a little bit more confusing the presentations of the different types of CMD overlap. The overlap is not only within CMD subtypes but also among other congenital muscular dystrophies, congenital myopathies, and limb-girdle muscular dystrophies. There is still benefit to using the umbrella term CMD because it provides a framework for the diagnostic approach to the infant or young child who presents with muscle weakness.

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What are the features of Congenital Muscular Dystrophy?

Signs of CMD include general muscle weakness and joint deformities. More severe forms of CMD may include severe mental and speech problems, and seizures. At least 30 different types of CMD are now recognized.

At first glance, the various types of CMD seem to have little in common other than their early onset. But on the molecular level, the types can be grouped by how their faulty protein affects the muscle cells. A very small group of CMDs are linked to proteins that affect what happens inside muscle fibers, affecting how the fibers process signals from the nervous system, for example, or how they handle calcium. But the vast majority of CMD types are related to proteins that make up or interact with the extracellular matrix that surrounds muscle fibers. Several types of CMD that arise from gene mutations that initially seemed unrelated now appear to be related to defects in proteins that "sugar-coat" (glycosylate) a matrix protein, allowing it to connect with other proteins. Several less known CMD subtypes have been reported in a limited number of individuals.

Several researchers have proposed classifications for CMD. The following scheme shows the currently accepted four categories of CMD with the known affected gene named in the brackets:

1. Defects in structural proteins
    a.Laminin-alpha2-deficient CMD (MDC1A)
    b. Ullrich CMD (UCMD 1, 2, 3)
    c. Integrin-alpha7 deficiency (Integrinalpha7)
    d.CMD with epidermolysis bullosa (Plectin)

2. Defects of Glycosolation
    a. Walker-Warburg syndrome (multiple genes)
    b. Muscle Eye Brain disease (multiple genes)
    c. Fukuyama CMD (Fukutin)
    d. CMD + secondary laminin deficiency 1 (MDC1B)
    e. CMD + secondary laminin deficiency 2 (fukitin related protein deficiency, MDC1C)
    f. CMD with mental retardation and pachygyria (mutation in LARGE, MDC1D)

3.Proteins of the endoplasmic reticulum and nucleus
    a. Rigid spine syndrome (Selenoprotein N, 1)
    b. Rigid spine syndrome (Selenocysteine insertion sequence-binding protein 2)
    c. LMNA-deficient CMD(Laminin A/C)

4.Mitochondrial membrane protein
    a.CMD with mitochondrial structural abnormalities (Choline kinase beta)

Laminin-alpha2-deficient CMD (MDC1A - Merosin-deficient congenital muscular dystrophy type 1A) is the most common CMD, and accounts for approximately 40% of all cases. Reduced fetal movements in utero may be noticed. At birth, patients may have low muscle tone (hypotonia), weakness, difficulties in feeding, and respiratory problems. Contractures are common. External ophthalmoplegia (paralysis of the motor nerves of the eye) may occur late. Most infants eventually sit unsupported, but standing is rare. Nerve disorders (demyelinating neuropathy) are common, and CNS manifestations may be present, such as mild mental retardation, seizures and structural brain changes. Weakness is usually static, or minimally progressive. Complications are related to respiratory compromise, feeding difficulties, scoliosis, and cardiopulmonary disease.

Typical features of **Ullrich CMD** include presentation in the neonatal period with hypotonia, kyphosis (curvature) of the spine, contractures, torticollis (twisting of the neck), and hip dislocation. Protruding heel bones (calcaneus) may be exhibited, as well as hyperlaxity of the joints. Kyphosis and the contractures may improve with therapy, and some patients will learn to walk in time, or with delay. However, this ability to move around independently will be lost after 2-10 years, usually due to recurring contractures. Respiratory insufficiency invariably develops within the first ten to twenty years. Children with CMD are often characterised by facial dysmorphism, including micrognathia, a round face with prominent ears and drooping of the lower lid. Brain function is normal, as is cardiac function.

Integrin-alpha7 deficiency is extremely rare; only three children in the world have been diagnosed with this condition.

Congenital muscular dystrophy with familial junctional epidermolysis bullosa
Since first being described in the 1970s, several more reports have described patients with epidermolysis bullosa a group of genetic conditions that cause the skin to be fragile and to blister easily and muscular dystrophy. Epidermolysis bullosa can be severe, even resulting in death and presents with severe blistering often secondary to

trauma or heat.Other skin findings can include nail dystrophy and scalp alopecia. Muscle weakness is proximal, progressive often leading to wheelchair use by the second decade and may correlate with residual plectin function. Other systemic features include growth retardation, anemia, larynx abnormalities, tooth decay, an obstruction in the lower stomach, infantile respiratory insufficiency, and cardiomyopathy. In some cases, skin manifestations are mild and may not cause significant disability. Presentation may then be as a late onset (20-40 y).

Walker-Warburg syndrome presents in utero or at birth with hypotonia, weakness in the feeding muscles (difficulties in sucking, swallowing), and contractures. This is a progressive disease, and the average time of death is nine months of age. Eye abnormalities such as retinal detachment and cataracts will lead to blindness. Brain abnormalities are severe and common.

Muscle Brain Eye (MEB) disease is variable in its severity. Severely affected children cannot sit or turn, and they lack visual contact. These children do not usually live past the first one to two years. Moderately affected patients can often sit, and speak a few words. They may have severe short-sightedness (myopia), but can make visual contact. Mildly affected children may be able to walk for a short time, they can speak in sentences, and they have good vision. Seizures are common in MEB disease, as is mild-to-severe mental retardation. Mild-to-severe brain changes are common and show up on an MRI. Hyrocephalus (excessive fluid in the brain) may need to be treated with the placement of a shunt.

Fukuyama congenital muscular dystrophy (FCMD) is usually picked up in utero, by poor fetal movements. A weak mouth and lack of head control is noticeable in the neonatal period. Between two and eight years of age, most children with FCMD can stand or walk a few steps, but some patients may require support to even sit. In most cases, cardiac disease develops after 10 years of age, resulting in cardiomyopathy and congestive heart failure. Eye abnormalities are present in about 50% of patients, and cerebral changes are always present, resulting in seizures for many patients. Severe mental retardation is present, although many children with FCMD do learn to talk. Death from muscular weakness and respiratory failure usually occurs mid-teens, although this varies from two to 25 years of age.

Children with defects in the **MDC1B** gene present in the first year with hypotonia and weakness. Motor milestones are delayed, but walking is achieved by three years. Facial weakness is prominent, and muscle hypertrophy is common. Respiratory failure

leads to death or the need for venitilatory assistance. Intelligence and brain MRIs are normal.

Defects in the **MDC1C** gene present with variable severity and symptoms. The severe end of the spectrum includes muscular dystrophy, eye abnormalities leading to blindness, and structural brain abnormalities. The typical form is similar to CMD with laminin-alpha2 deficiency (MDC1A). Presentation is at birth with hypotonia and weakness with delayed motor milestones. Some children with this disorder will be able to sit up, or take a few steps in the first decade of life, but progressive weakness leads to respiratory insufficiency and death, or ventilatory dependence. Hypertrophy of the tongue and legs will be noted, and facial weakness is usually present. Mild weakness of the heart can occur (cardiomyopathy). Intelligence and brain MRIs are normal. The mild form presents with characteristics similar to that of limb-girdle disease. With early-onset weakness, the ability to walk is lost in the teens, and subsequent scoliosis and ankle contractures occur. Muscle and tongue hypertrophy is common, and facial weakness is common. Teenagers will usually require ventilatory assistance, and respiratory failure is the most common cause of death. With late-onset (in teens or adulthood), walking and mobility can be preserved until the sixth or seventh decade, but respiratory insufficiency and failure may develop before then. Cardiomyopathy develops in 50% of patients with early- or late-onset weakness.

Defects in the **MDC1D** gene has been described in one case, a 17 year old female who presented with weakness and hypotonia at five months of age.

Rigid Spine Syndrome (RSMD) is apparent at birth, or within the first year of life with variable degrees of weakness and hypotonia. Most patients will eventually walk and maintain mobility for many years, and in contrast to Ullrich CMD, contractures are not present at birth, but usually develop between the ages of three and ten. Contractures may occur in the limbs, fingers and face. Children with RSMD1 are often characterised by spinal rigidity and scoliosis. Respiratory insufficiency is common and progressive. Ventilatory assistance at night may be needed as early as the first decade. The cardiac system is usually normal, and intelligence and brain function is not affected.

LMNA-deficient CMD This is caused by a mutation in the gene that encodes for proteins Laminin A/C. Mutations in LMNA cause a wide variety of disorders including Emery Drifuss Muscular Dystrophy.

Congenital muscular dystrophy with mitochondrial structural abnormalities. This syndrome is caused by a mutation in the choline beta kinase gene. Clinical

features present in most patients include hypotonia starting in early infancy, generalized muscle weakness, marked mental retardation with most not acquiring meaningful language, and microcephaly. Other features seen in some patients include dilated cardiomyopathy and dry, thickened, scaly or flaky skin.

What causes Congenital Muscular Dystrophy?

CMD is a genetic disease, caused by a fault in any number of different genes. Genes contain the recipe for proteins, and when faulty, may result in the reduction or complete absence of the protein. In the case of CMD, the proteins affected are muscle proteins. The reduction or loss of these muscle proteins create the characteristic symptoms of muscle wasting and weakness. Only about 25-50% of patients with CMD have an identifiable genetic mutation

CMD may be inherited, or it may arise spontaneously. Spontaneous or sporadic mutations occur randomly during a child's conception. When the mutation is inherited, it is usually in an autosomal recessive pattern. This means that the condition will only become apparent in a child if both parents carry the faulty gene, yet do not display symptoms. Other forms may be autosomal dominant, and one severe form is X-linked, affecting boy babies.

Diagnosis of Congenital Muscular Dystrophy

There are often difficulties in diagnosing CMD, as signs and symptoms of the disease vary. Where there is no family history, CMD is unlikely to be suspected straight away. The earliest sign of CMD is likely to be a 'floppy baby' – severe proximal weakness at birth or within twelve months of birth. Once CMD is suspected, diagnostic tests will be offered to establish a definite diagnosis. These may include:

• CK Testing
As in many of the muscular dystrophies, blood levels of the muscle enzyme creatine phosphokinase (CK, or CPK), may be increased. This enzyme is normally found in muscle cells. When the muscle cell is damaged, CK leaks out into the blood stream. A blood test will show elevated levels of CK, up to ten times that of normal.

• MRI
Magnetic resonance imaging (MRI) is a technique that is able to generate an image of the soft tissue in the brain. This allows visualization of the characteristic brain changes that occur with some CMD disorders.

• EMG
An electromyography (EMG) investigates the electrical activity of a muscle. In CMD, the EMG will typically show activity that is smaller and shorter than usual. Nerve conduction velocity (NCV) tests measure the speed with which a nerve is able to transmit information. This test is more accurate in the older child than in infancy.

• Muscle Biopsy
A muscle biopsy is required for diagnosis. Normal muscle fibres are regular in size; in CMD they may appear irregular, or poorly formed. There may be evidence of muscle degeneration and repair.

Soon after the diagnosis of a CMD child, it is essential that genetic counselling is arranged, for one or both of two issues. The first is the probability that the mutation was inherited from the parents; and the second is whether testing for the condition in future pregnancies can be offered, and with what degree of reliability.

• Genetic counselling provides information about possible diagnostic tests, including prenatal testing.

Management of Congenital Muscular Dystrophy

As yet, there is no cure for CMD. It is possible, however, to minimize the complications by adhering to a management programme specially designed by a team of medical professionals. The team will usually be headed by a paediatric specialist, and includes a physiotherapist, together with specialists in other areas as required.

• Exercise
Passive exercise, or assisted stretching, should be established as early as possible. It is valuable to have regular contact with a physiotherapist who can assist in the development of an exercise programme to delay the onset of contractures.

• Supportive Equipment
Braces and walking sticks may prolong mobility, but it is likely that a motorized or light-weight manual wheelchair will be required. An occupational therapist and/ or

seating therapist can advise on the most appropriate type of chair and supportive seating. It may therefore be wise to consider suitability of the home environment at an early stage, so that adjustments can be made over time to make it more wheelchair accessible.

• Nutrition
Excessive weight gain can occur due to reduced physical activity produced by the muscle weakness. Being overweight can place extra stress on already weak heart and bowel function, on joints, and also with breathing. It is therefore important that kilojoule intake reflect energy needs. Poor suckling in infancy may mean that feeding tubes are required. There should be no need for extra dietary supplement.

• Surgery
If contractures develop at the ankle joints, these can be surgically treated by release of the Achilles tendon. This helps improve foot position. Having a comfortable foot position may help prolong mobility for some CMD children. Spinal fusion surgery is performed to correct scoliosis. The medical team, including an Orthopaedic Surgeon and headed by the paediatrician, will discuss this option with the CMD boy and his family well before the surgery becomes necessary.

• Respiration
As muscles become gradually weaker, respiratory function starts to decline enough to produce changes in the way the lungs pull air in and push it out. Family and caregivers must watch carefully for signs of disrupted sleep due to respiratory problems. Signs include morning drowsiness, lack of concentration, headaches, confusion, sleepiness during the day and wakefulness at night with an increased need to be turned. When respiratory problems become apparent, ventilation machines are available to assist with ventilation during the night.

Research into Congenital Muscular Dystrophy

Research in the congenital muscular dystrophies centers around understanding the molecular processes that lead to muscle loss in these disorders and experimenting with methods to counteract these processes.
Among the approaches being tried in laboratory rodents is gene addition (insertion of new genes, sometimes called gene therapy or gene transfer), either to directly supply the missing protein or to supply proteins that can help compensate for a missing or abnormal protein.

A variant on this theme is blocking the activity of harmful genes, which is also being tried in lab models of CMD.
Another theme in CMD research is the need to fully understand the process of glycosylation of proteins, such as alpha-dystroglycan, in the muscle-fiber membrane. Glycoslyation of a protein means the addition of sugar molecules to the protein, which changes the way the protein interacts with other substances. Alpha-dystroglycan is not sufficiently glycosylated in several forms of CMD, so understanding and correcting this process is a promising avenue for treatment of these disorders. Several forms of CMD share three common muscle abnormalities:
• excessive apoptosis (also known as programmed cell death);
• inflammation; and
• fibrosis (scar tissue formation).

Drugs and other strategies that combat these processes are being tried in laboratory-based CMD research.

Support for people with CMD

Education
In New Zealand, every child has the right of equal access to all aspects of education. This means that all children with a neuromuscular condition have the right to attend a mainstream school. Many schools have special units attached which can provide any extra help needed, including an individualized education plan for appropriate assistance with physical and mental needs.

• It is important that children with CMD are not overprotected or patronized – they should be mentally stimulated and creative skills encouraged.
• A MDA Fieldworker can help by giving a presentation to the class and the MDA has a Teacher's guide that can help the teacher understand how having a neuromuscular condition may be impacting the child at school and ways to achieve their full potential.

Employment
There is no reason why a person with CMD should not expect to have the same employment opportunities as anybody else; however it is probably prudent to plan a career which will remain suitable even if physical ability declines.

Workbridge provides a professional employment service for all people with all types of disabilities and injuries, no matter what the disability or skill level. Workbridge also

administers support funding on behalf of Work and Income. Workbridge can be contacted on free phone: 0508 858 858 or through their website: www.workbridge.co.nz

More help on equal employment rights can be found on the Employment Relations website www.ers.dol.govt.nz. Employment Relations also has an infoline: 0800 800 863.

The government promotes equal employment opportunities (EEO) in private sector employment through the EEO Trust. They can be contacted on (09) 523 3023, or by visiting their website www.eeotrust.org.nz

Remember, it is illegal for employers to discriminate against people because of ethnicity, sexual orientation, gender, marital status, religious belief or disability. Equal rights are demanded by the Human Rights Act, 1993, and the Equal Pay Act, 1972.

More information

Muscular Dystrophy Association can be contacted for further information, assistance, advice, support and referrals, on 0800 800 337 or by e-mail at info@mda.org.nz

The Muscular Dystrophy Association Website also contains information on services available within NZ, our quarterly magazine, contacts, membership details, news and links to other sites - www.mda.org.nz

Further references

www.mdausa.org – the Muscular Dystrophy Association USA website has an extensive site with plenty of further information on any muscular dystrophy conditions as well as research news.

www.muscular-dystrophy.org – the UK muscular dystrophy site. It contains good general information on the condition.

NZ also has an excellent website dedicated to helping and informing those families with rare disorders – www.nzord.org.nz

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Information in this fact sheet was sourced from:

Muscular Dystrophy Canada - http://www.muscle.ca
http://mda.org/disease/congenital-muscular-dystrophy/ accessed on January 15 2015
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http://emedicine.medscape.com/article/1180214-overview accessed on January 16 2015
http://www.encyclopedia.com/topic/voluntary_muscle.aspx access on January 16 2015
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