What is Ullrich congenital muscular dystrophy?

Ullrich congenital muscular dystrophy is a hereditary muscle disorder often noticed at birth or within the first few months of life. It is one of at least 30 different types of congenital muscular dystrophy (CMD). Each type has a different genetic cause and a different range of symptoms, but they have two things in common: they are present at birth or soon after and primarily affect the muscles used for movement.

Children with Ullrich CMD have weak muscles, are often double jointed in their hands and feet and have stiffness in the spine and joints such as the elbows or hips. Breathing problems tend to develop which require ventilator support.

Ullrich CMD is caused by a change in one of the three collagen VI genes. This results in very little or no collagen VI protein being produced in the body. Different changes to the VI genes cause Bethlem myopathy which has less severe symptoms.

In this factsheet:

- What are the first signs?
- What are the symptoms of Ullrich CMD?
- What causes Ullrich CMD?
- Is Ullrich CMD inherited?
- How is Ullrich CMD diagnosed?
- What can be done to manage the condition?
- What research is being done?
- Further information

What are the first signs?

Babies with Ullrich CMD often have hypotonia (low muscle tone or floppiness), and may have reduced movements. Other common signs are hip dislocation and a stiff neck (torticollis) and tightness (contractures) in the hips, knees and elbows. Some babies may also have feeding problems, which improve after a few weeks or months.

Sometimes the first signs are only noted after a few months when babies are observed to have poor head control or have a delay in learning new skills such as sitting unaided.
What are the symptoms of Ullrich CMD?
There is a wide range of severity of this condition. Some children will learn to walk, albeit a bit later than their peers, whereas others are never able to walk independently but they may be able to stand and walk with leg splints.

In the first years, the condition is fairly stable and the child usually gains strength as he or she gets older. Motor function remains relatively stable but when children reach puberty, they might experience increasing difficulties, as muscles find it difficult to cope with the greater strain of increased weight and height. Those that walk independently may lose this ability at this stage.

While motor function remains relatively stable or only slowly progressive, children often develop breathing problems at night because the muscles used for breathing are affected. As breathing muscles weaken, chest infections may also become more frequent.

Children with Ullrich CMD may be born with or develop ‘contractures’, this means that the muscle tendons tighten up and the limbs and joints cannot be moved freely. Most of the children with Ullrich congenital muscular dystrophy also develop a curvature of the spine (scoliosis).

Another frequent problem after the first few years is weight loss (failure to thrive) which requires nutritional supplementation.

As collagen VI is also normally present in the skin, children may have a tendency for scars to heal slowly or become thickened and elevated (keloid formation).

There are measures that can be taken to manage the symptoms, please see ‘What can be done to manage the condition’ below.

What causes Ullrich CMD?
Ullrich CMD is caused by a change in one of the collagen VI genes (which are called COL6A1, COL6A2 and COL6A3). This usually results very little or no collagen VI protein being produced in in the body. Collagen is the main protein of connective (supporting) tissue in the body and provides support for the muscle cells. The exact mechanisms how these genetic changes lead to the disease are not fully understood but it is thought that as well as weakening the structure supporting muscle cells, the muscle cells are more sensitive to cell death and there might be a change in the energy supplying parts of the cells called mitochondria.

Is Ullrich CMD inherited?
Yes. The pattern of inheritance is known as ‘autosomal recessive’ which means that two copies of the altered gene are inherited – one from each parent. Both parents are carriers of the condition (although clinically unaffected) and they have a risk of 25%, or a one in four chance in each pregnancy, of passing the condition on to their children.
Occasionally a case may be ‘sporadic’ which means the fault in the gene is not inherited from the parents but instead may have arisen for the first time in the affected child.

All families with Ullrich congenital muscular dystrophy should be referred for genetic counselling. Genetic counselling provides information on the inheritance pattern, risks to other family members, and the ‘prognosis’ (likely outcome of the disorder). Options to minimise the risk of passing the condition on to future children can also be discussed such as “prenatal diagnosis” and “preimplantation genetic diagnosis”.

**How is Ullrich CMD diagnosed?**

The diagnosis of Ullrich congenital muscular dystrophy is usually suspected from the history and examination. The specific diagnosis however is generally made by examining a piece of muscle or skin (muscle and skin biopsy) under a microscope and genetic testing.

Before doing a muscle biopsy (which involves taking out a small piece of muscle, usually from the thigh) a few other tests may be done. One of these tests is a blood test, which measures the level of a muscle protein (creatine kinase or CK). However, in Ullrich CMD the levels of this protein are often normal or only mildly raised so the test may be used to rule out some other types of muscular dystrophy. Imaging such as ultrasound or MRI may detect a distinctive pattern of changes to the muscle which may point towards one particular type of muscular dystrophy.

These tests provide a broad indication that there is a muscle problem but cannot pin-point the precise diagnosis – a muscle biopsy or a genetic test is required for this.

The muscle biopsy sample is examined under a microscope and if a type of muscular dystrophy is present the muscle fibres, instead of being evenly sized, show a great variation
and some of these fibres are replaced by fat and fibrous tissue. Then specific coloured ‘tags’ which bind to collagen VI are used to detect how much collagen VI, if any, is present.

As collagen VI is normally present both in muscle and skin, taking a small piece of skin (skin biopsy) can also help to confirm the diagnosis. In some cases it is easier to detect a reduction of collagen VI on skin cells than on muscle cells. Taking a piece of skin however cannot provide some of the information that one can achieve with a muscle biopsy and it is therefore important to have both muscle and skin biopsies to obtain all the information needed.

Genetic tests looking for changes in one of the three genes responsible for Ullrich CMD are now available and provide the ultimate diagnosis. Genetic tests are usually done on a blood sample.

**What can be done to manage the condition?**
At the moment there is no cure for Ullrich congenital muscular dystrophy, but there are ways, described below, of helping to alleviate the effects of the condition, and research is underway to find a treatment.

Physiotherapy is one of the main forms of help. An initial physiotherapy assessment at the time of the diagnosis should be followed by an exercise/stretching program and regular check-ups. The main aim of physiotherapy is to keep the muscles as active as possible and to prevent the formation of contractures (muscle tendon tightness causing restriction in the range of joint movement). Early mobilisation in a standing frame is important to achieve upright posture and protect against the development of scoliosis and other contractures. When contractures do develop, surgery is sometimes required to release them. Children are encouraged to remain as active as possible. Swimming is a particular good form of exercise.

Physiotherapy can also help provide orthoses, such as splints and long leg callipers and a wheelchair when necessary. Occupational therapists can also help with the physical problems encountered in everyday living such as accessibility around the home and aids to help with tasks such as bathing.

Curvature of the spine (scoliosis) often develops in the first or second decade of life. It is important to provide a proper sitting and standing posture to prevent or delay curvature of the spine. If a curvature occurs a spinal brace may help to prevent further deterioration of the curvature. Scoliosis surgery might be needed in some cases.

Night-time breathing problems may happen in children of any age and, when present, children feel tired, often have headaches on waking in the morning, may feel sleepy during the day and lose appetite and weight. It is therefore very important to monitor for breathing problems on a regular basis. There are several breathing tests that may be done, one of which is a simple test which monitors level of oxygen throughout the night using a sensor attached to a finger or toe. If the level of oxygen recorded at night is not satisfactory, children will be referred to a respiratory physician who will provide a means of supporting breathing at night. This will involve a ventilator which pumps air in and out of the lungs via a
special facial or nasal mask. This is effective in reducing symptoms and improving quality of life.

When breathing muscles are weak, chest infections can be a problem. Therefore, pneumococcal (pneumonia) and annual influenza (flu) vaccines are recommended as well as early and aggressive use of antibiotics if an infection does develop. Chest physiotherapy, breathing exercises (breath stacking techniques) and equipment such as a cough assist machine may also be necessary to help clear secretions from the lungs.

It is important to monitor weight and height to be sure that children with Ullrich CMD receive enough food and energy. Feeding supplements are often needed under the direction of a nutrition specialist. Sometimes it is necessary to surgically insert a tube into the stomach (gastrostomy) to allow the child to receive enough calories and nutrients to maintain his or her weight.

A CMD family guide was published in 2010 which contains the medical management recommended by a group of 82 international experts from 7 medical subspecialties. The guide is for all types of CMD so some of the information may not be relevant, but detailed advice is given on all of the medical management measures described above. You can download “The Management of Congenital Muscular Dystrophy (CMD) - a guide for families” at the following website: http://www.curecmd.org/wp-content/uploads/resources/cmd-guide.pdf.

What research is being done?
In recent years researchers have discovered a lot about what is happening inside the cells of people with Ullrich CMD. One of the findings is that structures in the cells called mitochondria - which are the ‘batteries’ supplying energy - are not functioning correctly. This has led to several drugs that work on the mitochondria being tested in animal models of the conditions. Two drugs have shown promise - omigapil and Debio 025.

A company called Santhera is conducting a clinical trial of omigapil in the USA. This trial will involve children with CMD, including Ullrich CMD. Patient enrolment is expected to start in late 2014. More information is available at the following website: http://www.clinicaltrials.gov/ct2/show/NCT01805024

Debio 025 has been shown to restore mitochondrial function in muscle cells of patients grown in the laboratory and in a mouse model. Plans for a clinical trial in people with Ullrich CMD have not been announced.

Another possible avenue being considered for the development of therapies includes drugs that reduce 'fibrosis' or scarring in the muscles which is thought to be a major contributor to the muscle weakness in CMD. Losartan, a commonly prescribed medication for high blood pressure, is one possible candidate for testing in clinical trial as it has been shown to reduce fibrosis in mouse models of CMD.

These approaches that target the mitochondria and fibrosis do not address the root cause of the condition so would only be able to treat some of the symptoms of the condition. Ideally a treatment would result in the production of properly functioning collagen in the body. Gene therapy to correct
genetic mutations is being researched for other genetic conditions including muscular dystrophy and if these prove to be successful it may be possible to apply this technology to the development of treatments for Ullrich CMD.

You may be interested in registering with the Congenital Muscle Disease International Registry (CMDIR) (http://www.cmdir.org/). This is a patient registry: a database that contains information about patients with a particular condition. Clinical trial organisers and other researchers use this (anonymous) information to learn more about the conditions and plan clinical trials. If a clinical trial were to start, the registry would be used to contact suitable potential participants and invite them to take part. Patient registries are also a useful source of information for patients and their families as regular newsletters are sent out. You can find out more about patient registries on our website (http://www.mda.org.au/registries/index.asp).

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

- Read about the research MDA funds which aims to reduce inflammation in the muscles and improve muscle regeneration (http://www.nmdrc.org)
- For definitions of any terms that you are not familiar with please take a look at our glossary [http://www.mda.org.au/research/ResGlossary.asp]
- US based organisation CureCMD is a useful source of information relating to all types of CMD (http://curecmd.org/)
- 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:

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References

Muscular Dystrophy Campaign factsheet (www.muscular-dystrophy.org/information_resources/factsheets/medical_conditions_factsheets/ullrich.html)

