Muscular Dystrophy New Zealand

What is Emery-Dreifuss muscular dystrophy?

Emery-Dreifuss muscular dystrophy (EDMD) is a condition that mainly affects muscles used for movement (skeletal muscles) and heart (cardiac) muscle. It is named after Alan Eglin H. Emery and Fritz E. Dreifuss.

Among the earliest features of this disorder are joint deformities called contractures, which restrict the movement of certain joints. Contractures can become noticeable in early childhood and most often involve the elbows, ankles, and neck. Most affected individuals also experience slowly progressive muscle weakness and wasting, beginning in muscles of the upper arms and lower legs and progressing to muscles in the shoulders and hips. This disorder affects both sexes with first symptoms usually displayed between the ages of 17 and 40. A power chair or scooter or wheelchair may be needed by adulthood.

Almost all people with Emery-Dreifuss muscular dystrophy have heart problems by adulthood. In many cases, these heart problems stem from abnormalities of the electrical signals that control the heartbeat (cardiac conduction defects) and abnormal heart rhythms (arrhythmias). If untreated, these abnormalities can lead to an unusually slow heartbeat (bradycardia), fainting (syncope), and an increased risk of stroke and sudden death in affected people and carriers of the condition. Occasionally sudden cardiac arrest is the first symptom of the condition.

Varieties of Emery-Dreifuss muscular dystrophy

The types of Emery-Dreifuss muscular dystrophy are distinguished by their pattern of inheritance: X-linked, autosomal dominant, and autosomal recessive. Although the three types have similar signs and symptoms, researchers believe that the features of autosomal dominant Emery-Dreifuss muscular dystrophy are more variable than the other types. A small percentage of people with the autosomal dominant form experience heart problems without any weakness or wasting of skeletal muscles.

X-linked Emery-Dreifuss muscular dystrophy (X-Linked EDMD) is the most common form of this condition, affecting an estimated 1 in 100,000 people. The autosomal recessive type of this disorder appears to be very rare; only a few cases have been reported worldwide. The incidence of the autosomal dominant form is unknown.

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Causes of Emery-Dreifuss muscular dystrophy

Mutations in three different genes cause Emery-Dreifuss muscular dystrophy.

The EMD and LMNA genes provide instructions for making proteins that are components of the nuclear envelope, which surrounds the nucleus in cells. The nucleus is a compartment of the cell that contains the cell's genetic information. EMD codes for a protein called emerin and LMNA codes for two proteins lamin A and lamin C that associate with each other. The nuclear envelope regulates the movement of molecules into and out of the nucleus, and researchers believe it may play a role in regulating the activity of certain genes.

Lamin A and C are Nuclear lamins and are found in the cell's nucleus. They are fibrous proteins providing structural function as well as regulation in the cell nucleus during cell division.

FHL1 gene codes for a protein called Four and a half LIM domains protein 1. This protein is heavily produced in skeletal and muscle tissue.

Most cases of Emery-Dreifuss muscular dystrophy are caused by mutations in the EMD gene. This gene provides instructions for making a protein called emerin, which appears to be essential for the normal function of skeletal and cardiac muscle. Most EMD gene mutations prevent the production of any functional emerin. It remains unclear how a lack of this protein results in the signs and symptoms of EmeryDreifuss muscular dystrophy.

Emerin is a serine-rich nuclear membrane protein and a member of the nuclear lamina-associated protein family. It mediates membrane anchorage to the cytoskeleton.

Less commonly, Emery-Dreifuss muscular dystrophy results from mutations in the LMNA gene. This gene provides instructions for making two very similar proteins, lamin A and lamin C. Most of the LMNA mutations that cause this condition result in the production of an altered version of these proteins. Researchers are investigating how the altered versions of lamins A and C lead to muscle wasting and heart problems in people with Emery-Dreifuss muscular dystrophy.

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Inheritance

Depending on the specific gene defect that is causing the condition it is inherited in three ways which are described below:

X-linked recessive: The sex chromosomes X and Y determine if a baby will be a boy or a girl. X-Linked EDMD is caused by a defect in either the FHL1 or EMD gene on the X chromosome. One functioning copy is enough to prevent X-Linked EDMD. Girls receive an X from mum and an X from dad and are described as XX. Boys receive a Y from dad and an X from mum and are described as XY. As boys have only one X chromosome if they inherit an X chromosome with the defective EMD or FHL1 gene then they will have X-Linked EDMD. The mother is described as a carrier and with one functioning EMD gene is usually unaffected, although can have the related heart problems. A carrier mother has a 25% chance in each pregnancy of having an affected male child.

Autosomal dominant: The LMNA gene is located on chromosome 1 and is considered to have an autosomal dominant pattern of inheritance. This means that one defective copy is enough for the disease to present. Men and women are equally likely to be affected and that an affected person has a 50% chance in each pregnancy that their child will also be affected.

About 75 percent of autosomal dominant Emery-Dreifuss muscular dystrophy cases are caused by new mutations in the LMNA gene and occur in people with no history of the disorder in their family. In the remaining cases, people with this form of the condition inherit the altered LMNA gene from an affected parent.

Autosomal recessive: Rarely, LMNA gene mutations can cause a form of Emery-Dreifuss muscular dystrophy that is inherited in an autosomal recessive pattern. This means that both copies of the abnormal gene must be defective for the disease to develop fully. In this situation each parent is a carrier of one defective gene. Each child they have has a 25% chance of inheriting the disease.

Genetic counseling is available to families who have had a diagnosis of Emery-Dreifuss muscular dystrophy (as there are several different inheritance patterns it is important that the diagnosis is correct). This service provides information, helps families understand inheritance patterns and what this means in their family, as well as enabling people to make more informed family-planning decisions. You can access this via your GP, self-refer or an MDA Fieldworker.

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Diagnosis

As part of diagnosing this muscular dystrophy the Doctor may take a family history and conduct a physical examination. The Doctor will be trying to determine if the weakness is a problem with the muscles or the nerves that control them. Some special tests may be ordered to give more information and help with the diagnosis. The diagnosis of X-linked EDMD also relies on failure to detect emerin or FHL1 protein in various tissues and molecular genetic testing of EMD or FHL1. The diagnosis of autosomal dominant-EDMD and autosomal recessive-EDMD also relies on molecular genetic testing of LMNA.

Occasionally, special tests called nerve conduction studies and electromyography (EMG) are done. In these tests, electricity and very fine pins are used to stimulate and assess the muscles or nerves individually to see where the problem lies. Electromyography is uncomfortable but not usually very painful.

Early in the diagnostic process doctors often order a special blood test called a CK level. CK stands for creatine kinase, an enzyme that leaks out of damaged muscle. When elevated CK levels are found in a blood sample, it usually means muscle is being destroyed by some abnormal process, such as a muscular dystrophy or inflammation. Therefore, a high CK level often suggests that the muscles themselves are the likely cause of the weakness, but it doesn't tell exactly what the muscle disorder might be.

To determine which disorder is causing CK elevation, a doctor may order a muscle biopsy, the surgical removal of a small sample of muscle from the patient. By examining this sample, doctors can tell a great deal about what's actually happening inside the muscles. Modern techniques can use the biopsy to distinguish muscular dystrophies from infections, inflammatory disorders and other problems.

Other tests on the biopsy sample can provide information about which muscle proteins are present in the muscle cells, and whether they're present in the normal amounts and in the right locations. This can tell the doctor and patient what's wrong with the cells' proteins and provide likely candidates as to which genes are responsible for the problem. The correlation between missing proteins on the muscle biopsy and genetic flaws isn't perfect, however. An MDA clinic physician can help you understand these results. For example a diagnosis of x-linked EDMD would be confirmed if there was a lack or emerin or FHL1 protein detected.

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Genetic (DNA) tests, using a blood sample, can analyze the person's genes for particular defects that cause EDMD, help predict the likely course of a disease and help families assess the risk of passing on the disease to the next generation.

Management

There is a multidisciplinary team approach to management of the symptoms that present during the course of this condition. A neurologist, cardiologist, respiratory physician, physiotherapist, occupation therapist, orthopaedic surgeon and a dietitian may all be needed at some point. Make sure you are given referrals as things change so that the new symptoms are getting the best treatment available.

Specifically, surgery may be required to release contractures and to manage scoliosis (curvature of the spine) as required. Aids to assist in walking should be provided as appropriate e.g. canes, walkers, orthoses, wheelchairs. Treatment of the presenting heart problem which can include medication, pacemaker, implantable cardioverter defibrillator (ICD). Respiratory aids: muscle training, assisted cough techniques, assisted ventilation as needed.

Prevention of primary symptoms – physical therapy and stretching to prevent contractures. Implantation of cardiac defibrillators to reduce risk of sudden death.

A secondary complication can be cerebral thromboembolism (blood clot in the brain) experienced when the functioning of the left ventricle in the heart is decreased or atrial arrhythmias (rapid and irregular heart beat). This is treated with medication.

Surveillance: At a minimum, annual cardiac assessment which may include ECG, Holter monitoring and/or echocardiography. Also monitoring of respiratory function.

Agents/circumstances to avoid: Triggering agents for malignant hyperthermia, such as depolarizing muscle relaxants (succinylcholine) and volatile anesthetic medication (halothane, isoflurane) as well as obesity.

Relatives of people diagnosed with autosomal dominant EDMD and female carriers of X-linked EDMD should have cardiac evaluations as they may not have any other traits except heart issues.

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Research

Current research is looking at the following methods of treating muscular dystrophies:

• Gene therapy: a mechanism for supplementing defective genes with healthy genes in the tissues affected by neuromuscular disease;
• Gene silencing: turning off genetic instructions that cause the production of toxic proteins; and
• Cell therapy: transplanting new muscle cells, using stem cells or immature muscle cells from a donor or genetically corrected cells from the patient's own body.

Others are looking at ways to preserve muscle despite the presence of a degenerative disease.

Specific to EDMD researchers are studying the interactions that emerin and the lamin proteins have and the various "downstream" effects of genetic mutations that cause EDMD, with an eye to identifying targets for treatment development. And currently there are tests on medications to treat the specific heart problems associated with EDMD in mouse models of the disease.

Support

The MDA Fieldworkers are available for support. They have in-depth knowledge of a range of neuromuscular conditions, and will have a better understanding of your needs and challenges. Have a chat over the phone or they can come to you for a kanohi ki te kanohi/face-to-face visit. They may have some real practical suggestions that have worked for others to offer as well. This service is offered free of charge to MDA members and is funded through donations and grants. Contact your local MDA Branch to be put in contact with your fieldworker.

The MDA Support Network allows people with similar circumstances or challenges to come together to share their experiences and provide each other with emotional and moral support in addition to practical advice and information. By bringing together people with common experiences, support networks can provide an invaluable addition to medical care. The MDA of New Zealand Support Network currently has over 600 members throughout New Zealand who want to be in touch with others livings with neuromuscular conditions. Please see the MDA website www.mda.org.nz for contact details and more information that you might find relevant for you and your whanau.

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