X-Linked Myotubular Myopathy

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Synonyms of X-Linked Myotubular Myopathy

- MTM
- myotubular myopathy
- XLCNM
- x-linked centronuclear myopathy
- XLMTM

General Discussion

Summary

X-linked myotubular myopathy (XLMTM) is a rare genetic neuromuscular disorder that is characterized by muscle weakness that is most typically severe but can range from mild to profound. Symptoms are often present at birth, though may develop later in infancy or early childhood. Rarely, symptoms may not present until adolescence or adulthood. Common symptoms include mild to profound muscle weakness, diminished muscle tone (hypotonia or "floppiness"), feeding difficulties, and potentially severe breathing complications (respiratory distress). Feeding difficulties and respiratory distress develop because of weakness of the muscles that are involved in swallowing and breathing. The overall severity of the disorder can range from mildly affected individuals to individuals who develop severe, life-threatening complications during infancy and early childhood. Most affected individuals have a severe form of the disorder and respiratory failure is an almost uniform occurrence. XLMTM is caused by mutations to the myotubularin (*MTM1*) gene. The disorder is inherited as an X-linked condition. The disorder predominantly affects males, but female carriers, while typically asymptomatic, can develop a range of symptoms. In rare specific cases, females can develop a severe form similar to that seen in males.

Introduction

XLMTM belongs to a larger group of disorders known as the centronuclear myopathies. In addition to XLMTM, there are forms of centronuclear myopathy that are inherited as autosomal dominant or autosomal recessive conditions. Generally, the autosomal forms are less severe than XLMTM; however, in rare cases, individuals with an autosomal form can develop severe complications that are similar to those seen in XLMTM. Centronuclear myopathies derive their name from the abnormal location of the nucleus in the center of the muscle fiber (muscle cell) rather than its normal position on the edge. Additional pathologic features include disorganized perinuclear organelles and abnormalities in oxidative staining patterns. Centronuclear myopathies can be further classified into the larger, broader category of congenital myopathies, a group of genetic muscle disorders that are present at birth.

In the medical literature, centronuclear myopathy is generally used for the autosomal forms of the disorder and myotubular myopathy is generally used for the X-linked form. Distinguishing between the X-linked (myotubular) form and the autosomal forms is essential as the symptoms are usually more severe in the X-linked form. NORD has a separate report on centronuclear myopathy that describes the autosomal forms in greater detail. This report specifically deals with X-linked centronuclear (myotubular) myopathy.

Signs & Symptoms

The specific symptoms and severity of XLMTM can vary greatly from one person to another, though the majority of individuals with MTM have a severe presentation. While the disorder may be fatal during infancy or childhood, some affected individuals will only develop mild to moderate symptoms. Because of the variable nature of XLMTM, parents should talk to their child's physician and medical team about their specific case, associated symptoms and overall prognosis.

One classification subdivides XLMTM into a severe (classic) form, a moderate form and a mild form. Most affected individuals have the severe (classic) form of XLMTM. Moderate and mild forms of XLMTM are far less common. In the severe form, affected male infants exhibit extreme muscle weakness and hypotonia (floppiness) at or shortly after birth. Weakness of the muscles used to breathe and swallow can cause respiratory distress and feeding difficulties during infancy often noticeable within the first few days or weeks of life. Respiratory distress can be present at birth and can cause affected infants to require constant, prolonged ventilation during infancy. Affected infants may be unable to suck, swallow or breathe on their own. In the U.S., the initial hospital stay for surviving infants is approximately 90 days.

Some children with XLMTM will die during the first few months or years of life. Other individuals will survive this initial period but require 24 hour ventilator, feeding, and wheelchair support. However, other individuals will become independent of a ventilator or only require periodic assisted ventilation such as during sleep. A proportion of affected individuals will survive into the teenage years and beyond. Of note, long-term ventilation during infancy carries risks including recurrent infection, inadequate shallow breathing (hypoventilation), and lack of oxygen in the blood (hypoxia).

Muscle weakness and poor muscle development can also cause delays in the attainment of motor milestones. Most affected individuals are unable to walk (non-ambulatory). Muscle weakness associated with XLMTM is not believed to be progressive, but this has not been definitely confirmed. Individuals with XLMTM often grow tired more easily than their peers.

Affected infants often have distinctive facial features including a high forehead, underdevelopment of the middle of the face (midface hypoplasia), weakness of facial muscles, and a disproportionately long and narrow head (dolichocephaly) with a long face. Some infants have a narrow, high-arched roof of the mouth (palate) and later on develop severe misalignment of the teeth (malocclusion). Partial or complete paralysis of one or more of the muscles that control the movements of the eye (ophthalmoparesis) is also common. Drooping of the upper eyelids (ptosis) and nearsightedness (myopia) may also occur.

In some individuals, growth parameters may be abnormal. In general, head circumference is larger than would be expected based on age and gender (macrocephaly). Affected infants may be in the 90th percentile for length at birth. Weakness of the facial muscles is often very obvious.

Additional symptoms may occur including abnormally long fingers and toes, absence of reflexes (areflexia), and shortening or hardening of tissue that causes deformity and restricts movements of affected areas, especially the joints (contractures). Failure of the testes to descend into the scrotum (cryptorchidism) may also occur. As affected individuals grow older, more symptoms can occur including fractures of the long bones, malformation of the hip (hip dysplasia) and abnormal side-to-side curvature of the spine (scoliosis). Scoliosis can worsen respiratory problems and cause individuals who no longer require assisted ventilation to go back onto ventilator support. In some cases, advanced bone age and premature production of sex hormones called androgens (premature adrenarche) has also been reported.

Many long-term survivors with severe XLMTM require a wheelchair and need assistance for normal daily activities. A variety of additional low incidence complications have been reported in long-term survivors. Such complications include narrowing of the outlet that connects the stomach to the small intestine (pyloric stenosis), gallstones, kidney stones, mild anemia due to the formation of abnormal red blood cells (spherocytosis), bleeding abnormalities, and liver dysfunction. Some individuals develop peliosis hepatitis, a liver condition characterized by randomly located, multiple blood-filled cavities throughout the liver. This condition can cause life-threatening bleeding (hemorrhaging) episodes.

Cognitive development and intelligence are usually unaffected, except in extremely rare cases or in individuals who suffer a significant hypoxic episode, in which the brain is deprived of oxygen.

Mild and Moderate Myotubular Myopathy
Some individuals may have milder forms of the disorder. The moderate form of XLMTM is generally characterized by similar signs and symptoms to the severe form. However, individuals will have longer periods of time where the need for ventilator support is decreased. In addition, affected individuals will attain motor milestones faster than individuals with the severe form.

Individuals with the mild form of XLMTM only experience slight delays in attaining motor milestones and most achieve the ability to walk. These individuals may only require ventilator support in the newborn period. Some individuals with the mild form do not have the characteristic facial features that are seen in the severe form of XLMTM, and often also have eye movement paralysis.

Individuals with mild or moderate XLMTM are at risk for breathing problems including especially nocturnal hypoventilation and sleep apnea. In addition, respiratory decompensation can develop when dealing with an unrelated illness. This may require a return to or an increase in ventilator support.

At least three multigenerational families have been described in the medical literature with male family members who developed mild cases of XLMTM, sometimes not developing symptoms until adulthood.

Causes

XLMTM is caused by a mutation in the myotubularin (*MTM1*) gene. Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a mutation of a gene occurs, the protein product may be faulty, inefficient, or absent. Depending upon the functions of the particular protein, this can affect many organ systems of the body.

XLMTM is inherited as an X-linked genetic disorder. X-linked genetic disorders are conditions caused by a gene change on the X chromosome. Females have two X chromosomes but one of the X chromosomes is "turned off" and all of the genes on that chromosome are inactivated. This is a normal process known as random X-chromosome inactivation. Females who have a disease gene change present on one of their X chromosomes are carriers for that disorder. Carrier females usually do not display symptoms of the disorder because the X chromosome with the abnormal gene change is "turned off" in approximately 50% of the cells of the body. A male has one X-chromosome and if he inherits an X chromosome that contains a disease gene change, he will develop the disease. Males with X-linked disorders pass the disease gene change to all of their daughters, who will be carriers if the other X chromosome from their mother is normal. A male cannot pass an X-linked gene to his sons because males always pass their Y chromosome instead of their X chromosome to male offspring. Female carriers of an X-linked disorder have a 25% chance with each pregnancy to have a carrier daughter like themselves, a 25% chance to have a non-carrier daughter, a 25% chance to have a son affected with the disease, and a 25% chance to have an unaffected son. In a minority of cases, a mutation in the *MTM1* gene that causes the disorder occurs randomly for no apparent reason (de novo mutation). In these cases, the mother is not a carrier and the risk of recurrence of the mutation in a subsequent pregnancy is extremely low.

As a result of random X-chromosome inactivation, most females with a *MTM1* mutation do not develop symptoms, although some females will exhibit mild symptoms such as mild weakness of certain muscles. In extremely rare cases, females can develop a severe form of XLMTM similar to the one seen in males. This may be due to a skewing of the inactivation of the X-chromosome without the gene change; therefore the majority of the instructions for the myotubularin protein come from the X-chromosome with the gene change.

In a few children recently reported in the medical literature, male children with XLMTM developed the disorder not because of a mutation, but because of a duplication involving the *MTM1* gene. A duplication is a structural chromosomal abnormality in which a portion of the X chromosome appears three times in the cells of the body instead of twice. Researchers believe that some cases in which individuals have XLMTM but do not have a mutation of the *MTM1* gene are caused by a duplication of the X chromosome involving the *MTM1* gene. There is also now evidence for changes/mutations at the *MTM1* gene locus that occur outside of the protein making region but that impact the processing of the MTM1 RNA.

Investigators have determined that the *MTM1* gene is located on the long arm (q) of the X chromosome X (Xq28). Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated "p" and a long arm designated "q". Chromosomes are further sub-divided into many bands that are numbered. For example,

“chromosome Xq28” refers to band 28 on the long arm of the X chromosome. The numbered bands specify the location of the thousands of genes that are present on each chromosome.

The *MTM1* gene creates (encodes) a protein known as myotubularin. This protein is believed to be critical for the proper development, maintenance, and function of muscle tissue. The exact, specific functions of this protein are not fully understood, though recent work has suggested in plays a role in maintaining aspects of muscle structure including the part of the muscle fiber responsible for excitation-contraction coupling, which is a normal process involved in skeletal muscle contraction. A mutation in the *MTM1* gene leads to low levels of functional myotubularin.

Affected Populations

XLMTM primarily affects males. Some carrier females may develop mild symptoms associated with the disorder. The exact incidence of the disorder is unknown, but one estimate places it at 1 in every 50,000 male births in the general population. It is the most common form of centronuclear myopathy.

Related Disorders

Symptoms of the following disorders can be similar to those of XLMTM. Comparisons may be useful for a differential diagnosis.

XLMTM belongs to a group of disorders known as centronuclear myopathy (CNM). Other types of CNM include an autosomal dominant form and three autosomal recessive forms, known by the mutated gene associated with each form. Currently, one primary autosomal dominant form has been identified and is known as DNM2-related CNM. Three autosomal recessive forms have been identified and are known as RYR1-related CNM, BIN1-CNM, and *SPEG* related CNM (found only in a small number of families. Of note, a small number of individuals with *BIN1* mutations have been discovered to have autosomal dominant CNM. Some individuals with CNM do not have mutations in any of these genes, suggesting that additional genes may cause autosomal forms of CNM. The autosomal forms are generally less severe than X-linked myotubular myopathy and usually do not display abnormal growth parameters. However, the severity of the autosomal forms can vary dramatically from one person to another. In some cases, individuals with an autosomal form can develop severe complications and a presentation that is very similar to severe XLMTM. (For more information on these disorders, choose “centronuclear myopathy” as your search term in the Rare Disease Database.)

Congenital myopathy is a group of muscle disorders (myopathies) where symptoms are typically present at birth (congenital). These conditions are typically distinguished from other early-onset muscle disorders (such as the congenital muscular dystrophies and congenital myotonic dystrophy) by features on muscle biopsy, creatine phosphokinase (CPK) levels in the blood, and genetic testing results. These disorders are characterized by muscle weakness, low muscle tone (hypotonia), diminished reflexes, and delays in reaching motor milestones (e.g., walking). In some disorders, muscle weakness is progressive. The severity of these disorders can range from mild to those associated with severe, life-threatening complications. This group of disorders includes nemaline myopathy, central core disease, congenital fiber type disproportion, minimulticore myopathy, and the centronuclear myopathies. Congenital myopathies are usually apparent in the newborn (neonatal) period, but may present much later in life, even in adulthood.

In most cases, inheritance of these disorders is either autosomal recessive or autosomal dominant or X-linked. Of note, congenital myotonic dystrophy can clinically resemble severe CNM and may contain a CNM-like pattern on muscle biopsy. Therefore, this disease is an important condition to consider in the differential diagnosis of MTM. (For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database.)

Congenital myasthenic syndromes are a group of rare genetic disorders characterized by abnormalities affecting the neuromuscular junction, which is the point where the nerve and muscle cells meet. The underlying defect in these disorders can involve the nerve cell, the muscle cells, or the space in between. These disorders are characterized by muscle weakness and fatigue of the skeletal muscle. Onset is usually at birth or during infancy or early childhood. The severity of these disorders is highly variable, ranging from mild symptoms to severe, disabling symptoms. Symptoms that can be associated with these disorders include respiratory insufficiency or distress, feeding difficulties, paralysis of eye movements, drooping of the upper eyelids (ptosis), and multiple joint contractures. Affected infants and children may exhibit delays in attaining motor milestones. They may fatigue rapidly from normal activities such as climbing stairs or running. Additional symptoms are usually present as well. Because of the overlapping signs and symptoms between CNMs and congenital myasthenic syndromes, and because of the fact that many congenital myasthenic syndrome patients respond favorably to specific therapies, it is always important to consider these conditions in the differential diagnosis of centronuclear myopathy. Congenital myasthenic syndromes can be inherited as autosomal recessive conditions or, less frequently, as autosomal dominant conditions.

Myotonic dystrophy type 1 (DM1) is an autosomal dominant, multi-system disorder that affects both smooth and skeletal muscles and may affect the central nervous system, heart, eyes, and/or endocrine systems. There are three types of DM1 that are distinguished by the severity of disease and age of onset. Mild DM1 is characterized by cataracts and sustained muscle contractions (myotonia). Classic DM1 is characterized by muscle weakness and wasting (atrophy), cataracts, myotonia and abnormalities in the heart's conduction of electrical impulses. Congenital DM1 is characterized by muscle weakness (hypotonia), difficulty breathing, intellectual disability and early death. (For more information choose "myotonic dystrophy" as your search term in the Rare Disease Database.)

Diagnosis

XLMTM should be suspected in newborns with hypotonia and muscle weakness and older male children with weakness in the arms and legs and diminished muscle bulk. A diagnosis is based upon identification of additional characteristic symptoms (e.g. cryptorchidism, long fingers and toes, macrocephaly), a detailed family history, a thorough clinical evaluation, and a variety of specialized tests.

Clinical Testing and Workup

A muscle biopsy may be performed to aid in obtaining a diagnosis. A biopsy involves surgical removal of a small sample of affected muscle tissue and examining the sample under a microscope. This allows physicians to note the characteristic, microscopic changes to muscle tissue, specifically the presence of the nucleus in the center of the muscle fiber (muscle cell) rather than toward the edge.

A diagnosis of XLMTM is confirmed through molecular genetic testing, which can detect mutations in the *MTM1* gene causative of the disorder. Molecular genetic testing can detect a mutation in approximately 60%-98% of affected individuals and is available on a clinical basis.

Standard Therapies

Treatment

The treatment of XLMTM is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists with expertise in treating neuromuscular disorders. Pediatricians, pulmonologists, neurologists, orthopedists, eye specialists, dental specialists, and other healthcare professionals may need to systematically and comprehensively plan an affect child's treatment. Genetic counseling will be of benefit for affected individuals and their families.

The treatment of affected individuals usually requires intensive medical intervention. Some affected individuals will require prolonged, constant ventilation support. There are different methods for ventilation including noninvasive and invasive techniques. The decision about the duration of respiratory support is best made by the family in careful consultation with the patient's physicians and other members of the healthcare team based upon the specifics of their case.

In some individuals feeding difficulties will require the insertion of a feeding tube (gastrostomy). This procedure involves inserted a tube directly into the stomach through a small surgical opening in the abdominal wall.

Physical and occupational therapy is recommended to improve muscle strength and prevent contractures. Special measures may be necessary to allow ventilator-dependent individuals to communicate. Additional therapies are symptomatic and supportive. For example, scoliosis may require surgical intervention.

Investigational Therapies

Gene therapy is being studied as an approach to therapy for XLMTM. The discovery of the *MTM1* gene in 1998 has enabled researchers to explore this potential therapy. In gene therapy, the defective gene present in a patient is replaced with a normal gene to enable the produce of the active enzyme and prevent the development and progression of the disease in question. Given the permanent transfer of the normal gene, which is able to produce active enzyme at all sites of disease, this form of therapy is theoretically most likely to lead to a "cure". Studies of *MTM1* gene therapy in both mouse and dog models of MTM have shown great promise, and clinical trial of this treatment strategy is planned in the near future. However, at this time, such clinical studies are required before gene therapy can be advocated as a viable alternative approach.

Another consideration is protein replacement therapy. Studies utilizing the mouse model of MTM have demonstrated that systemic injection of a genetically engineered (recombinant) MTM1 protein can prevent disease onset and progression in this model.

Studies are underway to determine whether treatments aimed at the neuromuscular junction – the point where nerve cells and muscle cells meet – can help individuals with XLMTM. Researchers are studying the use of drugs that target proteins of the neuromuscular junction. Initial studies on

zebrafish and mice (murine) models have shown significant improvement in fatigable weakness. Much more research, including human trials, are required to determine whether this potential therapy has a role in the treatment of individuals with XLMTM.

The Joshua Frase Foundation maintains the International Family Registry for Centronuclear and Myotubular Myopathies. The purpose of this new registry is to create an investigator-patient relationship in order to allow researchers to better understand CNM/MTM and locate subjects for clinical trials. The following individuals are eligible to be registered:

Individuals affected with centronuclear myopathy (CNM)
Individuals affected with X-linked myotubular myopathy (XLMTM)
Female carriers of XLMTM

More information is available here: https://www.joshuafrase.org/research/get-involved/global-map.php

Currently, there is an ongoing prospective natural history study of individuals with XLMTM. This study is designed to elucidate and define specific features of the disease over time and to help identify potential outcome measures for future interventional trials. Also, there are multiple patient registries for MTM, including a disease specific registry organized through the Myotubular Trust and a registry encompassing all congenital muscle diseases (called the CMDIR) that includes XLMTM. Patients and families are encouraged to register through either registry mechanism:

Congenital Muscular Dystrophy International Registry (CMDIR)
Phone: 800.363.2630
Fax: 310.872.5374
Email: counselor@cmdir.org
Website: www.cmdir.org

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website: https://rarediseases.org/for-patients-and-families/information-resources/news-patient-recruitment/

For information about clinical trials sponsored by private sources, contact: www.centerwatch.com

For information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/