

# A Case Study: Myotubular Myopathy

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## Keywords:

**Centronuclear Myopathy**

**X-linked Recessive**

**Autosomal Recessive**

**Autosomal Dominant**

**Hypotonia**



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## **Abstract**

Myotubular Myopathy (MTM) is one of the rarer forms of Muscular Dystrophy. A genetically heterogeneous muscle disease, it has been described as an X-linked, an autosomal recessive, and an autosomal dominant trait. The very severe X-linked form is the most common variant and is characterized by severe loss of muscle tone and generalized muscle weakness, resulting from the inability of the muscle fibers to develop normally. X-linked MTM is characterized by early onset and the prognosis is usually not promising. Surviving infants born with this disease develop at a much slower pace, tend to be long and slender, and have limited movement. This report illustrates the different forms of MTM and highlights its effect on one particular family.

## **Abbreviations**

ENMC -- European Neuromuscular Center

MTM -- Myotubular Myopathy

## **Introduction**

The myotubular myopathies, also known as centronuclear myopathies, are among the group of rare myopathies called the congenital myopathies. This is due to their presence at birth as a congenital anomaly or defect. Myotubular myopathy is considered a disorder of muscle maturation. The term originates from the resemblance of the muscle fibers to the myotubular stage of muscle differentiation in fetal life. During this stage of development, myofilaments are characterized by centrally placed nuclei and the central

areas of the muscle fibers are devoid of myofibrils with aggregation of mitochondria (Wallgren-Pettersson, 1995).

Three different kinds of MTM have been recognized—X-linked, autosomal recessive, and autosomal dominant—and are differentiated mainly in terms of the mode of inheritance, onset, and severity. More is known about X-linked MTM than the other forms, and the X-linked myotubularin gene has been confined to a small area on the lower portion of the human X chromosome. Pre-natal diagnosis is possible if geneticists can trace the history of the disease in a family through a process called linkage analysis. Males are the victims of this type of MTM, and the prognosis has historically been considered to be very poor because many lack the sufficient muscles to breathe independently and withstand respiratory complications. Thus, the respiratory aspect of the disease remains the focus of treatments. Patients who have accepted major interventions, such as a tracheotomy or ventilator, have an increased chance of survival. There is presently no cure for MTM, and though research efforts are underway in the USA and Europe, the discovery of an effective cure is not in the foreseeable future.

Children diagnosed with X-linked MTM have been known to develop other disorders including spherocytosis (a disorder of the red blood cells that makes people more susceptible to anemia, hemolysis, enlargement of the spleen, reticulocytosis, and mild jaundice), peliosis of the liver (cysts form and can cause massive internal bleeding if ruptured), scoliosis (spinal curvature), and others (Myotubular Myopathy Resource Group, 2000). Other symptoms include a long and slender body, long fingers and toes, elongated head, shifting of bones due to poor muscle tone, and frog-leg posture. Affected individuals also have difficulty swallowing, and thus drooling is a consequence. For this

reason, most patients also cannot be fed orally and intake nutrients via feeding tubes or G-tubes. In addition, patients often suffer from reduced blinking during the day and partial eye closure while sleeping due to lack of sufficient muscle tone. This malady can be treated, however, with eye drops.

Doctors and researchers agree that a muscle biopsy is the most effective method of diagnosing patients with MTM. A muscle biopsy is a minor surgical procedure that involves making an incision in the skin to obtain a few small pieces of the underlying muscle for detailed histologic, histochemical, or biochemical examination (Department of Neurology, 2000).

## **Discussion**

### *Three Different Types of MTM*

The genetic origin of a disease is crucial to understanding the cause and developing specific treatments. There are three different types of MTM that are characterized by their pattern of inheritance, age at onset, and severity and prognosis.

Table 1.1 summarizes the differences in the three different types of MTM.

**Table 1.1** Summary of the three different types of myotubular myopathy, including a description of each, onset of symptoms, and clinical features. (Information taken from a book entitled *Neuromuscular Diseases: A Practical Approach to Diagnosis and Management*, 1997)

Type	Description	Onset	Clinical Features
X-Linked	Most common and most severe; affects males; abnormal X chromosome	Neonatal	hypotonia, respiratory weakness, often fatal
Autosomal Recessive	Affects males and females equally; both copies of a non-sex Chromosome gene are abnormal in affected child	Infancy and early Childhood	paralysis of the motor nerves of the eye, delayed motor milestones, mild generalized Weakness
Autosomal Dominant	Affects males and females equally; requires only one abnormal copy of a gene on a non-sex chromosome to have the disease	Late onset	proximal weakness

Females have two X-chromosomes, and thus have two copies of every gene. If one gene is dysfunctional, the other can compensate and normal development can occur. Males, on the other hand, have one X-chromosome and one Y-chromosome, and thus have one copy of every gene. If a female passed an abnormal or mutated X-chromosome onto her son, he would have no good copy of the gene to compensate the dysfunctional gene and would ultimately develop a genetic disorder. Male-to-male transmission cannot occur in X-linked dominant pedigrees.

To understand autosomal dominant and autosomal recessive inheritance, it is important to be familiar with a few concepts. First, since an individual has only two chromosomes with one copy of each gene, there are four possible allele combinations. An individual can have two normal alleles, one normal and one abnormal allele, two abnormal alleles, or one each of two different abnormal alleles. The phenotype, or the

property of the individual in which the gene operates, can be normal or abnormal. In both autosomal dominant and autosomal recessive inheritance patterns, those with two normal alleles have the normal phenotype and those with two abnormal alleles have the abnormal phenotype. The difference between the dominant and recessive patterns lies in the phenotype of those with one normal and one abnormal allele. In these individuals, if the abnormal phenotype is expressed, meaning that they have symptoms or physical evidence of the disorder or clinical tests are abnormal, the disorder is dominant. If the normal phenotype is expressed, the disorder is recessive (Rowland, 1989).

Autosomal dominant inheritance is vertical or hereditary, spanning successive generations. Children of an affected parent have a 50% chance of receiving the harmful gene and being affected with the disorder. Male-to-male transmission is possible.

Autosomal recessive inheritance, on the other hand, is horizontal or familial, affecting only that individual's immediate family. The parents, though not directly affected by the disorder, are both carriers, each having one normal and one abnormal allele. Each child has a 25% chance of being affected and a 50% chance of being a carrier. Males and females are affected with equal frequency and with equal severity, and it has been proven that recessive disorders show ethnic predilections.

#### *Symptoms of X-Linked Recessive MTM*

Affected male infants with X-linked MTM have severe hypotonia (a condition of diminished tone or tension, in this case involving muscles) and muscle weakness associated with respiratory failure. In addition, common findings associated with this type of MTM include cryptorchidism (a developmental defect characterized by failure of

one or both of the testicles to descend into the scrotum, instead they are retained in the abdomen or inguinal canal), joint contractures (an abnormal and usually permanent condition of a joint, characterized by flexion and fixation and caused by atrophy and shortening of muscle fibers or by loss of the normal elasticity of the skin), ptosis (an abnormal condition of one or both upper eyelids in which the eyelid drops because of a congenital or acquired weakness of the levator muscle or paralysis of the third cranial nerve), and high-arched palate (structure that forms the roof of the mouth) (Anderson, 1998). X-linked MTM is often fatal in the absence of ventilator support.

Results of a study conducted by Maries Joseph, G. Shashidhar Pai, Kenton R. Holden, and Gail Herman reveal that the majority of patients examined, who suffered from X-linked MTM, had a large head at birth, a weak cry, swallowing difficulties, a long body size, long digits, severely limited activity, and were ventilator dependent. Most infants with this disease do not survive past their first year of life (Joseph, et. al., 1995).

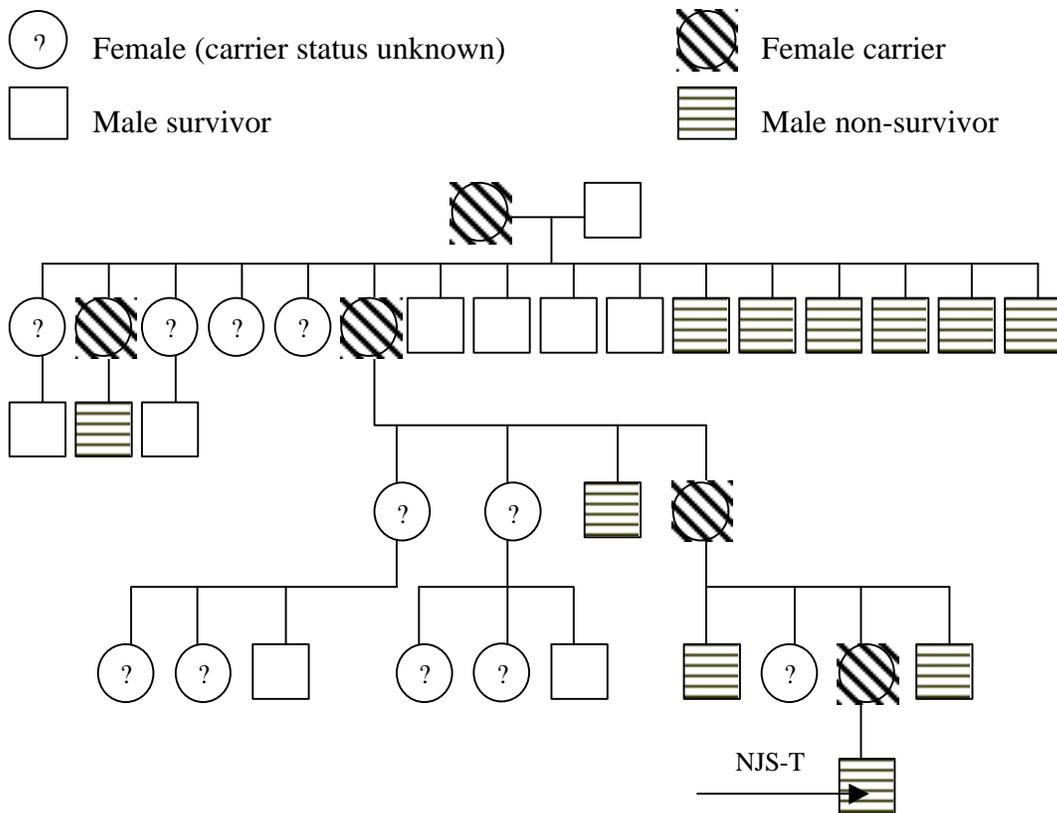
*A Case Study: Nathaniel Joseph Supleo-Tordesillas*

A baby boy affected with MTM was born to a healthy 20-year old mother on May 16, 1998. Upon delivery, the infant, named Nathaniel Joseph Supleo-Tordesillas, had a blue skin-color, was floppy, and had a large mucus plug that kept him from breathing and prevented doctors from intubating him. He was immediately rushed to the Hospital for Sick Children--a health care, teaching and research center dedicated exclusively to children and affiliated with the University of Toronto. Doctors were able to stabilize and

intubate him and a series of extensive tests were conducted in hopes of determining the cause of his symptoms.

The baby's grandmother was a carrier of the X-linked recessive gene for MTM and had previously lost two sons. In 1975 her first son lived for 1 hour, and in 1984 her second son lived for three weeks. The first boy was born in the Philippines, and due to lack of knowledge, equipment, and technology, his cause of death was unknown. The second boy, however, spent his short life at the Hospital for Sick Children, so the doctors dealing with Nathaniel were familiar with the family's history. Figure 1.1 presents a brief history of MTM's role in this particular family.

**Figure 1.1** Family history of Nathaniel Joseph Supleo-Tordesillas' family. The box furthest down on the right hand side represents Nathaniel.



The doctors did not want to assume that Nathaniel's case was MTM-related until they had ruled out all other possibilities, and three weeks later after a muscle biopsy had been completed and analyzed, Nathaniel was diagnosed with MTM. The prognosis was that he would not live; he was ventilator dependent and did not have the muscles to breathe on his own. Doctors predicted that he would survive no more than one week without the ventilator. Nathaniel was extubated on June 17, 1998, exactly one month and one day after his birth. But to everyone's surprise, he lived much longer than one week.

After 3 days without a ventilator, Nathaniel's oxygen and color were still good and he was transferred to Credit Valley Hospital because of its proximity to the home of his immediate family. Two weeks later, still going strong, Nathaniel finally went home and his parents were taught how to properly feed and suction him.

One of the effects of MTM is the inability to swallow properly. Thus, Nathaniel was fed through a feeding tube that went up his nose, down his throat, and into his stomach. His body's reaction to this foreign object was the secretion of more saliva, which increased the chances of him choking. Because he could not swallow, saliva was periodically suctioned out of his mouth and small towels were placed beside his mouth at all times to absorb his drool. Due to a lack of muscle tone, Nathaniel experienced a shift in his bones; his ribs on his right side jutted out like a mountain, and though it was difficult to look at, doctors assured that it did not cause him pain. Figure 1.2 displays more of Nathaniel's symptoms and clearly illustrates his condition.

**Figure 1.2** Nathaniel Joseph Supleo-Tordesillas. These pictures display some of the symptoms of MTM, such as a long and slender body, long fingers and toes, elongated head, shifting of bones due to poor muscle tone, frog-leg posture, and swallowing difficulties.



By September, only 4 months after his birth, the family began to see significant improvements in Nathaniel's condition. He was able to open and close his hands, pick up a rattle (considered heavy for a baby with MTM), kick when he laughed, and smile when he recognized people. He was a smart baby, and it was obvious that his disease did not affect his brain. Research has shown that the brain matures normally as long as the infant has not been deprived of oxygen for a long period of time during the birth and initial stabilization process (Myotubular Myopathy Resource Group, 2000).

The next milestone in this infant's young life was the G-tube operation that took place in November of 1998. The advantages of a G-tube were increased comfort, less irritation to the throat, which led to a decrease in the amount of saliva secreted, and feeding him via a tube that went directly to his stomach. The need to suction him was significantly reduced after the G-tube replaced his original feeding tube. During this operation, Nathaniel was not sedated because of the risk of him not waking up. Instead, doctors froze the small area of his stomach that was operated on.

Approximately one month later, problems arose. On December 17, 1998, Nathaniel's breathing pattern changed. His breathing was more staggered and characterized by gasps, and he cried all morning due to some form of irritation. The main problem occurred after his next feeding. He threw up everything he was fed, and most of it aspirated in his lungs. Nathaniel was rushed to the hospital and by 2 A.M. he began having seizures. Doctors confirmed that his trembling was a sign of his body shutting down. By 8:30 A.M., his skin color was no longer blue but gray and he was gasping for air. His breaths became more and more spread out and by 9 A.M. he had stopped breathing. Nathaniel was pronounced dead at 9:35 A.M. on December 18 when his heart officially stopped beating.

*A life so young released to heaven, left on earth we wonder "why,"  
But some are sent among us briefly, some have spirits meant to fly.*

### *Research Efforts*

Due to the rarity of this disease, existing research efforts are sorely lacking. However, workshops of the European Neuromuscular Center (ENMC) International Consortium on Myotubular Myopathy bring together scientists from eight countries. Focuses for these workshops have included diagnostic criteria for X-Linked MTM, refinement of the linkage region and the identification of candidate genes, cloning and characterization of the myotubularin gene, and mutations found in the myotubularin gene and their correlation with the clinical picture in boys affected by X-linked MTM. One interesting study is the canine model presented by Dr. Stephane Blot of Paris, France. He has observed a canine inherited neuromuscular disorder exhibiting traits of autosomal recessive MTM. Participants of the 58<sup>th</sup> ENMC workshop agreed that this canine disease resembles MTM in man (Wallgren-Pettersson, 1998).

Present research efforts include studying X-inactivation in females belonging to families with X-linked MTM, the spectrum of muscle biopsy features of affected boys in relation to age and type of mutation, further studies of the canine model, isolating substrates of myotubularin and eventually of myotubularin gene products. In addition, efforts are underway towards the completion of a diagnostic protocol.

## References

Anderson, Kenneth N. and Lois E. Anderson. Mosby's Pocket Dictionary of Medicine, Nursing, and Allied Health. New York: Mosby, 1998

This book was useful in defining some of the medical terms found in various journal articles and publications, especially pertaining to the symptoms of X-linked recessive MTM.

Department of Neurology, Baylor College of Medicine. *Muscle Biopsy*. URL: <http://www.bcm.tmc.edu/neurol/research/nmus/nmus4b.html>, March 21, 2000.

This article provides a comprehensive overview of muscle biopsy, including purpose, procedure, its usefulness, and diagnostic protocols.

Herman, GE, et al. "Medical Complications in Long-Term Survivors with X-Linked Myotubular Myopathy." Journal of Pediatric Health Care 134 (1999): 206-214.

X-linked mtm is a rare developmental disorder of skeletal muscle. Until recently, the disorder was usually fatal within the first year of life. This article deals with a study that was conducted to determine the outcome in long-term survivors (greater than 1 year of age). The results indicate that though some long-term survivors are at risk for potentially life-threatening medical complications involving other organ systems, the prognosis for X-linked mtm is not as poor as many believe. The results also suggest that the function of the MTM1 protein is not limited to developing muscle cells.

Maries, J., et al. "X-Linked Myotubular Myopathy: Clinical Observations in Ten Additional Cases." American Journal of Medical Genetics 59 (1995): 168-173

This article reports on 10 additional cases of severe neo-natal mtm from six different families, recording observations and comparing symptoms and effects of the disease.

MDA Diseases. *Myotubular Myopathy (MTM or MM)...A Guide to Related Materials on MDA's Web Site*. URL: <http://www.mdausa.org/disease/mm.html>, January 26, 2000.

This site has a lot of general information, but of greater importance for this paper, it provides a series of research links like Research Digest, Gene Therapy Information, descriptions of clinical trials and studies of possible treatments for MDA-covered diseases, recent research developments, major medical/research sites, and recommended readings.

Myotubular Myopathy Resource Group. *Myotubular Myopathy Resource Group*. URL: <http://www.mtmrg.org>, January 25, 2000.

This site is very thorough, offering links to articles, family stories, contact information, and descriptions of treatments and interventions. This site also provides a discussion group for those interested in learning more, as well as support for people who have been affected by MTM, either directly or indirectly. (The person who created this site was very helpful when I was grieving over the death of my nephew...he has provided me with contacts for doctors at UC-Northridge and Helsinki, as well as requested a copy of my paper upon completion so he can post it on this site.)

Rowland, Lewis P., et al. Molecular Genetics in Diseases of Brain, Nerve, and Muscle. New York: Oxford University Press, 1989.

This is a compilation of papers written by various authors. Sections are separated into four categories: 1.) background, 2.) the language and tools of molecular genetics, 3.) cloned genes for human neurological diseases, 4.) social policy and molecular genetics.

Samson, F., et al. "Genetic Linkage Heterogeneity in Myotubular Myopathy." American Journal of Human Genetics 57 (1995): 120-126.

To date, published linkage studies have provided no evidence of genetic heterogeneity in severe neo-natal myotubular myopathy. This article deals with an investigation of a family with typical severe neo-natal mtm in which no linkage to DNA markers was found. This suggests genetic heterogeneity in mtm and indicates that great care should be taken when using particular markers in linkage studies for prenatal diagnosis and genetic counseling.

Schwartz, Martin S. and Michael Swash. Neuromuscular Diseases: A Practical Approach to Diagnosis and Management. 1981. Ed. London: Springer, 1997.

The aims of this book are to correlate the different categories of information about neuromuscular diseases into an account that allows clinicians to understand their patients' problems, and to plan appropriate investigation and management. This edition takes into account new knowledge and technological advancements.

Tsai, CH, et al. "X-Linked Recessive Myotubular Myopathy Proven by Muscle Biopsy." J Formos Med Assoc 95 (1996): 153-156.

This report illustrates the importance of taking a detailed family history as well as a muscle biopsy in the diagnosis of X-linked recessive mtm, focusing on a baby boy who displayed most of the symptoms of mtm before passing 54 days after his birth.

Wallgren-Pettersson, Carina, et al. "The Myotubular Myopathies: Differential Diagnosis of the X-Linked Recessive, Autosomal Dominant, and Autosomal Recessive Forms and Present State of DNA Studies." Journal of Medical Genetics 32 (1995): 673-679.

The three forms of mtm differ in terms of age at onset, severity, prognosis, and some of the clinical characteristics. Though muscle biopsies and immunohistochemical staining are useful in making distinctions, determining the mode of inheritance and prognosis in individual families poses a problem.

Wallgren-Pettersson, Carina, et al. "58<sup>th</sup> ENMC Workshop: Myotubular Myopathy 20-22 March, 1998, Naarden, The Netherlands" Neuromuscular Disorders (1998): 521-525.

This article discusses collaborative work of the ENMC International Consortium on Myotubular Myopathy, bringing together specialists and scientists from eight countries. Previous workshop reports are mentioned, as well as directions for future collaborative work.