

FLOPPY BABY? It could be XLMTM

Differential Diagnosis for Neuromuscular Disorders, *Neonatal Onset*



Neuromuscular Disorder	Description	Clinical Findings	Muscle Fiber Status	Diagnosis*
<p>X-linked myotubular myopathy (XLMTM)</p> <p><i>X-linked recessive inheritance</i></p>	<p>A monogenic disorder caused by mutations in the <i>MTM1</i> gene encoding myotubularin, a protein required for muscle development, cellular organization, and function¹</p> <p>Onset typically at birth but atypical patients can present in childhood and later²</p>	<p>Characterized by profound hypotonia and respiratory insufficiency at birth³. Frequently accompanied by^{3,4}:</p> <ul style="list-style-type: none"> • Facial weakness (myopathic face) • Dolichocephaly • Bulbar weakness • Ophthalmoparesis, often associated with ptosis • Long fingers and toes • Frog leg position with abducted hips and flexed knees • Areflexia 	<p>Central nuclei. Muscle fiber atrophy and necrosis usually absent⁵</p>	<p>Genetic testing to confirm pathogenic or likely pathogenic variants in the <i>MTM1</i> gene³</p> <p>Historically muscle biopsy has been used in the differential diagnosis of XLMTM.^{4,5}</p>
<p>Spinal muscular atrophy, Type 1 (SMA Type 1)</p> <p><i>Autosomal recessive inheritance</i></p>	<p>A monogenic disorder caused by biallelic mutations in <i>SMN1</i> gene encoding SMN protein, which is essential for motor neuron survival and function⁶</p> <p>Loss of SMN leads to motor neuron loss in the spinal cord and brain stem, impairing muscle control⁶</p> <p>Onset typically before 6 months of age⁶</p>	<p>Characterized by progressive muscle weakness, lack/regression of motor development and poor muscle tone before 6 months of age⁷. Frequently accompanied by:</p> <ul style="list-style-type: none"> • Expressive face • Respiratory insufficiency • Bulbar weakness 	<p>Muscle fiber atrophy and muscle wasting due to motor neuron degeneration and loss⁷</p>	<p>Genetic testing to confirm mutations in the <i>SMN1</i> gene, as well as newborn screening programs^{6,7}</p>
<p>Myotonic dystrophy, Type 1 (DM1)</p> <p><i>Autosomal dominant inheritance</i></p>	<p>A monogenic disorder caused by trinucleotide repeat expansion in the <i>DMPK</i> gene, leading to build-up of toxic <i>DMPK</i> RNA which interferes with proper activity of various proteins important for muscle function⁸</p> <p>Typically later onset, but may also present in infancy (see details about later onset of DM1 on page two of this document)</p>	<p>In neonates, characterized by some combination of^{8,9}:</p> <ul style="list-style-type: none"> • Hypotonia • Respiratory insufficiency • Difficulty feeding • Facial weakness • Generalized weakness affecting skeletal, smooth muscle, eye, cardiac • Positional malformations including club foot 	<p>Central nuclei. Muscle fiber atrophy (particularly of Type 1 fibers), no necrosis¹⁰</p>	<p>Genetic testing to detect CTG repeat expansion within <i>DMPK</i> gene; number of repeats correlates with severity and age of onset⁹</p> <p>>1000 repeats – Congenital neonatal or early childhood onset</p>
<p>Prader-Willi syndrome (PWS)</p> <p><i>Spontaneous; very rarely inherited</i></p>	<p>A genomic imprinting disorder (caused by inheriting both chromosome copies from same parent, not by mutation) caused by loss of expression of multiple genes in chromosome 15¹¹</p> <p>Neonatal onset¹²</p>	<p>Characterized by profound hypotonia and bulbar weakness in early infancy¹¹. Followed in later infancy/early childhood by:</p> <ul style="list-style-type: none"> • Delayed motor milestones & language development • Some degree of cognitive impairment • Areflexia • Almond-shaped eyes • Excessive eating • Hypogonadism which manifests as genital hypoplasia, incomplete pubertal development and in most, infertility 	<p>Normal¹¹</p>	<p>DNA methylation testing to detect abnormal parent-specific imprinting within the disease-causing region of chromosome 15 (the PWCR region)¹¹</p>

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Differential Diagnosis for Neuromuscular Disorders, *Childhood or Adult Onset*

Neuromuscular Disorder	Description	Clinical Findings	Muscle Fiber Status	Diagnosis*
<p>Duchenne muscular dystrophy (DMD)</p> <p><i>X-linked recessive inheritance</i></p>	<p>A monogenic disorder caused by mutations in <i>DMD</i> gene encoding dystrophin protein, leading to dysfunction, degeneration, and necrosis of muscle fibers¹³</p> <p>Onset typically in childhood, primarily affects males, but female carriers may show symptoms¹⁴</p>	<p>Characterized by progressive muscle weakness (both skeletal and cardiac) in childhood, not infancy¹⁴. Frequently accompanied by:</p> <ul style="list-style-type: none"> • Delayed motor milestones • Difficulties in language • Cardiac issues 	<p>Degenerating and necrotic muscle fibers increasingly replaced by fibrosis and fatty tissue accumulation as the disease progresses¹⁴</p>	<p>Elevated creatine kinase (CK) concentration in serum</p> <p>Genetic testing to confirm mutation in <i>DMD</i> gene¹⁴</p>
<p>Myotonic dystrophy, Type 1, (DM1) (later onset)</p> <p><i>Autosomal dominant inheritance</i></p>	<p>A monogenic disorder caused by trinucleotide repeat expansion in the <i>DMPK</i> gene, leading to build-up of toxic <i>DMPK</i> RNA that interferes with proper activity of various proteins important for muscle function⁸</p> <p>Onset typically as teenagers⁸</p>	<p>In adults, characterized by⁹:</p> <p>Classic</p> <ul style="list-style-type: none"> • Muscle weakness (mostly distal in extremity muscles) • Cardiac issues • Posterior subcapsular cataracts <p>Mild:</p> <ul style="list-style-type: none"> • Mild myotonia & cataract <p>Note: Neonatal signs and symptoms on front page</p>	<p>Central nuclei.</p> <p>Muscle fiber atrophy (particularly of Type 1 fibers), no necrosis¹⁰</p>	<p>Genetic testing to detect CTG repeat expansion within <i>DMPK</i> gene; number of repeats correlates with severity and age of onset⁹</p> <p>~100 – 1000 repeats – Classic, early adulthood onset</p> <p>50 – ~150 repeats – Mild, adult onset</p>
<p>Congenital myasthenia syndrome (CMS)</p> <p><i>Typically autosomal recessive inheritance, rarely autosomal dominant</i></p>	<p>Monogenic disorder caused by mutations in various genes; all mutations lead to dysfunction of the neuromuscular junction¹⁵</p> <p>Onset typically within first 2 years of life, but can present at any age¹⁵</p>	<p>Characterized by muscle weakness, worsened upon exertion/ fatigable weakness¹⁵. In some patients, accompanied by:</p> <ul style="list-style-type: none"> • Facial weakness • Bulbar weakness • Ptosis • Double vision • Hypernasal or slurred speech 	<p>Normal¹⁵</p>	<p>Decremental EMG response of the compound muscle action potential on low frequency stimulation¹⁵</p> <p>In most cases but not always, positive response to acetylcholinesterase (AChE) inhibitors¹⁵</p> <p>Absence of anti-acetylcholine receptor (AChR) and anti-muscle-specific receptor tyrosine kinase (MuSK) antibodies in serum¹⁵</p> <p>Lack of improvement after immunosuppressive therapy¹⁵</p> <p>Multi-gene panel testing to identify disease-causing mutation¹⁵</p>

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