FLOPPY BABY? It could be XLMTM

Differential Diagnosis for Neuromuscular Disorders, ***Neonatal Onset***

Neuromuscular Disorder	Description	Clinical Findings	Muscle Fiber Status	Diagnosis*
X-linked myotubular myopathy (XLMTM) ***X-linked recessive*** *inheritance*	A monogenic disorder caused by mutations in the *MTM1* gene encoding myotubularin, a protein required for muscle development, cellular organization, and function[1] Onset typically **at birth** but atypical patients can present in childhood and later[2]	Characterized by **profound hypotonia** and **respiratory insufficiency *at birth*[3]**. Frequently accompanied by[3,4]: · 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	Central nuclei. **Muscle fiber atrophy and necrosis usually absent[5]**	Genetic testing to confirm mutations in the *MTM1* gene[3] Historically muscle biopsy has been used in the differential diagnosis of XLMTM.[4-6]
Spinal muscular atrophy, Type 1 (SMA Type 1) ***Autosomal recessive*** *inheritance*	A monogenic disorder caused by biallelic mutations in *SMN1* gene encoding SMN protein, which is essential for motor neuron survival and function[6] Loss of SMN leads to motor neuron loss in the spinal cord and brain stem, impairing muscle control[6] Onset typically **before 6 months** of age[6]	Characterized by **progressive muscle weakness, lack/ regression of motor development and poor muscle tone *before 6 months of age*[7]**. Frequently accompanied by: · Expressive face · Respiratory insufficiency · Bulbar weakness	**Muscle fiber atrophy and muscle wasting** due to motor neuron degeneration and loss[7]	Genetic testing to confirm mutations in the *SMN1* gene, as well as newborn screening programs[6,7]
Myotonic dystrophy, Type 1 (DM1) ***Autosomal dominant*** *inheritance*	A monogenic disorder caused by trinucleotide repeat expansion in the *DMPK* gene, leading to build-up of toxic *DMPK* RNA which interferes with proper activity of various proteins important for muscle function[8] **Typically later onset,** but may also present in infancy (later onset details on back page)[8]	In neonates, characterized by some combination of[8,9]: · Hypotonia · Respiratory insufficiency · Difficulty feeding · Facial weakness · Generalized weakness affecting skeletal, smooth muscle, eye, cardiac · Positional malformations including club foot	Central nuclei. **Muscle fiber atrophy** (particularly of Type 1 fibers), no necrosis[10]	Genetic testing to detect CTG repeat expansion within DMPK gene; **number of repeats correlates with severity and age of onset[9]** >1000 repeats – **Congenital**; neonatal or early childhood onset
Prader-Willi syndrome (PWS) ***Spontaneous;*** *very rarely inherited*	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 15[11] **Neonatal onset**[12]	Characterized by **profound hypotonia and bulbar weakness** in ***early infancy*[11]**. Followed in later infancy/early childhood by: · 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	Normal[11]	DNA methylation testing to detect abnormal parent-specific imprinting within the disease-causing region of chromosome 15 (the PWCR region)[11]

For more information, please visit xlmtm.com

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

Neuromuscular Disorder	Description	Clinical Findings	Muscle Fiber Status	Diagnosis*
Duchenne muscular dystrophy (DMD) ***X-linked recessive*** *inheritance*	A monogenic disorder caused by mutations in *DMD* gene encoding dystrophin protein, leading to dysfunction, degeneration, and necrosis of muscle fibers[13] Onset typically **in childhood**, primarily affects males, but female carriers may show symptoms[14]	Characterized by **progressive muscle weakness (both skeletal and cardiac) in childhood**, not infancy[14]. Frequently accompanied by: · Delayed motor milestones · Difficulties in language · Cardiac issues	**Degenerating and necrotic muscle fibers** increasingly replaced by fibrosis and fatty tissue accumulation as the disease progresses[14]	Elevated creatine kinase (CK) concentration in serum Genetic testing to confirm mutation in *DMD* gene[14]
Myotonic dystrophy, Type 1, (DM1) (later onset) ***Autosomal dominant*** *inheritance*	A monogenic disorder caused by trinucleotide repeat expansion in the *DMPK* gene, leading to build-up of toxic DMPK RNA that interferes with proper activity of various proteins important for muscle function[8] Onset typically **as teenagers**[8]	In adults, characterized by[9]: **Classic**: · Muscle weakness (mostly distal in extremity muscles) · Cardiac issues · Posterior subcapsular cataracts **Mild**: · Mild myotonia & cataract ***Note:*** *Neonatal signs and symptoms on front page*	Central nuclei. **Muscle fiber atrophy** (particularly of Type 1 fibers), no necrosis[10]	Genetic testing to detect CTG repeat expansion within *DMPK* gene; **number of repeats correlates with severity and age of onset**[9] ~100 – 1000 repeats – **Classic**, early adulthood onset 50 – ~150 repeats – **Mild**, adult onset
Congenital myasthenia syndrome (CMS) *Typically* ***autosomal recessive*** *inheritance, rarely autosomal dominant*	Monogenic disorder caused by mutations in various genes; all mutations lead to dysfunction of the neuromuscular junction[15] Onset typically **within first 2 years of life**, but can present at any age[15]	Characterized by muscle weakness, worsened upon exertion/ fatigable weakness[15]. In some patients, accompanied by: · Facial weakness · Bulbar weakness · Ptosis · Double vision · Hypernasal or slurred speech	Normal[15]	Decremental EMG response of the compound muscle action potential on low frequency stimulation[15] In most cases but not always, positive response to acetylcholinesterase (AchE) inhibitors[15] Absence of anti-acetylcholine receptor (AChR) and anti-muscle-specific receptor receptor tyrosine kinase (MuSK) antibodies in serum[15] Lack of improvement after immunosuppressive therapy[15] Multi-gene panel testing to identify disease-causing mutation[15]

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