Congenital Myopathies:

Clinical Presentation, Diagnosis, and Management

MDA® Muscular Dystrophy Association

Congenital Myopathies: Clinical Presentation, Diagnosis, and Management

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Program Objectives

- Recognize signs and symptoms of congenital myopathies
- Incorporate best practice guidelines for the management of patients
- Identify clinical trial opportunities
- Locate additional tools and resources

Program Agenda

1. Overview & Classification
2. Clinical Presentation
3. Pathophysiology
4. Diagnosis
5. Management
6. Clinical Research
7. Resources

Congenital Myopathies: Overview

Congenital myopathies are a group of hereditary rare neuromuscular disorders characterized by muscle weakness and hypotonia[1,2]

Description[2,3]

- Clinically, histopathologically, and genetically **heterogeneous**
  - **Variants** in the **same gene** can cause **different** muscle **pathology**
  - **Same genetic variant** can lead to **different features** within the **same family** or individual at **different ages**
- Clinically characterized by **hypotonia** and **weakness**
- Historically **classified** based on major **morphological features** seen on **muscle biopsy**

Epidemiology[3,4]

- Prevalence is **1** in **26,000**
- Cause of **14%** of all **neonatal hypotonia** cases

Onset and prognosis[3]

- Symptom **onset** is often at **birth or infancy**
- **Slow progressing** with stable clinical course
- **Life expectancy** varies depending on type and severity[5]
  - **Adolescent/adult-onset forms:** Normal life expectancy, loss of ambulation after age 50
  - **Birth-onset forms: Short** life expectancy (**<1 year,** eg, X-linked centronuclear types, nemaline myopathy)

1. Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382. 2. North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116. 3. Claeys KG. *Dev Med Child Neurol*. 2020;62(3):297-302.
4. Huang K, et al. *Front Neurol*. 2021;12:761636. 5. Cassandrini D, et al. *Ital J Pediatr*. 2017;43(1):101.

Myopathological History

Dr R.D.K. Reye
Description of “rod-like fragments” in a muscle biopsy of a 3-year-old boy

1958

1955

Nosography evolution

- Central core myopathy
- Nemaline myopathy
- Centronuclear myopathy

1970

Consolidation and expansion era

The nosological spectrum of the “classical” congenital myopathies expanded

- Clinically
- Myopathologically
- Genetically

1990

Genetic era

New nosographic element

- Congenital myopathy without disease-specific myopathological lesion and named after its mutant gene

Goebel HH, Stenzel W. *Neuromuscul Disord.* 2023;33(12):990-995.

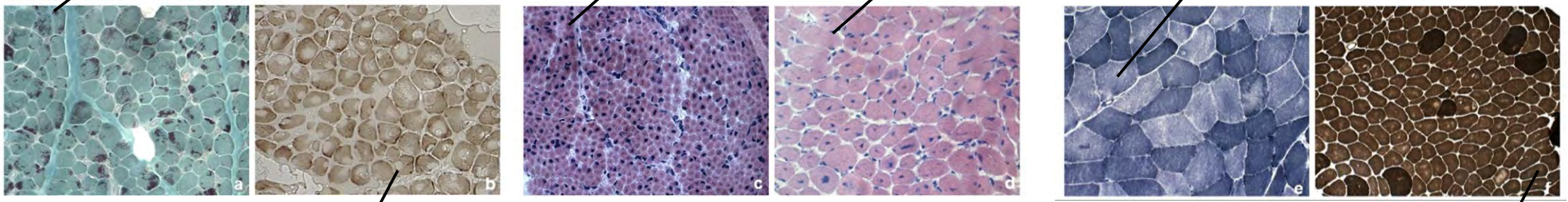
Classifications[1,2]

Histopathological approach

Nemaline rod myopathy (nemaline rods)

Centronuclear myopathies (central nuclei)

Myosin storage myopathy (multiminicores)



Core myopathy

Congenital fiber type disproportion

Figures from Cassandrini 2017. Open Access (CC BY-4.0)

Genetic approach

- Molecular testing is in constant evolution
- Classification based on causative gene
  - For example, *RYR1*-related myopathy

1. North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116. 2. Cassandrini D, et al. *Ital J Pediatr*. 2017;43(1):101

Classification – Genetic

27 congenital myopathy–causing genes

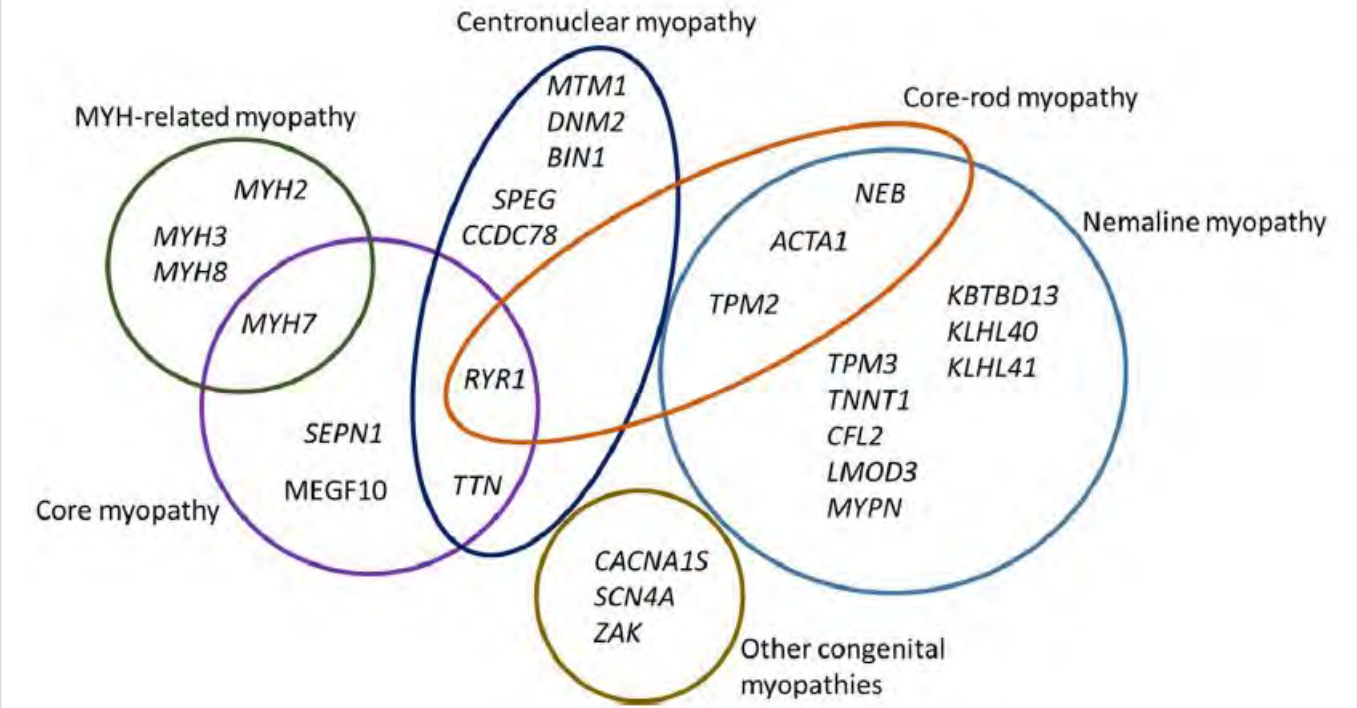


Figure from Pelin 2019. Used with permission from Elsevier.

Genetic basis of classification

- Congenital myopathies have overlapping causative genes and clinical features
- Inheritance can be autosomal dominant, autosomal recessive, or X-linked

Pelin K, Wallgren-Pettersson C. *Semin Pediatr Neurol.* 2019;29:12-22.

Common Clinical Features

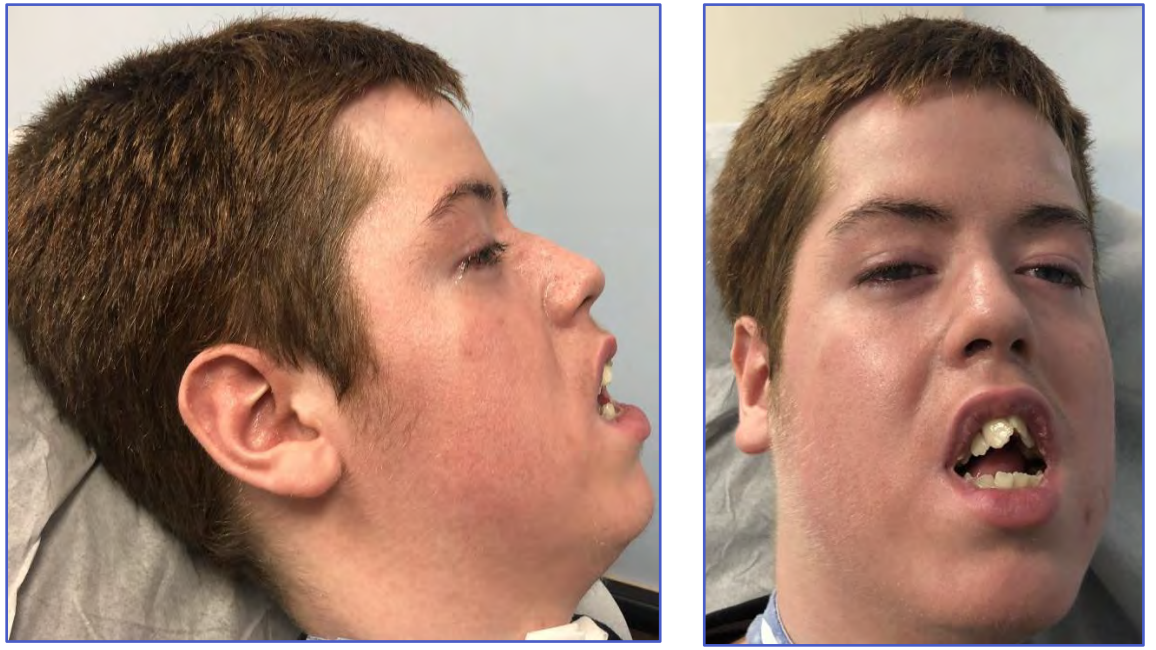
Phenotypes vary, but generalized muscle weakness is a common feature[1]

Common presentations[2,3]

- Generalized weakness
- Hypotonia (“frog-leg”)
- Decreased muscle bulk
- Hyporeflexia
- Myopathic face
  - Dysmorphic facial features
  - Arched palate and micrognathia

- Sensation is intact[1]
- Intelligence is usually normal[1]

Dysmorphic facial features in patient with congenital myopathy



Photos courtesy of Drs Batley, Gonzalez, and Iannaccone.

1. North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116. 2. Cassandrini D, et al. *Ital J Pediatr*. 2017;43(1):101. 3. Claeys KG. *Dev Med Child Neurol*. 2020;62(3):297-302.

Nemaline Myopathies

More common
Weakness of limbs, trunk, and facial muscles
Stable or slowly progressive disease course

Neonatal onset (16% of all cases)
Hyposthenic, hypotonic,
difficulty sucking and swallowing

Mild → **Severe**

Genetic etiology[1-3]

- 14 genes involved; most encode proteins associated with thin filaments in sarcomeres

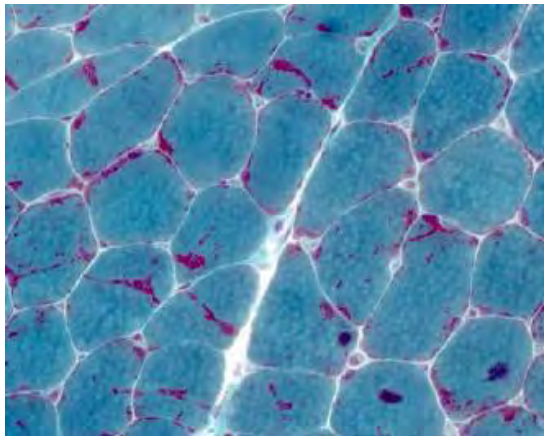
NEB	*TNNT3*	*RYR3*
ACTA1	*TPM2*	*KBTBD13*
LMOD3	*TPM3*	*ADSSL1*
KLHL41	*CFL2*	*TNNT1*
KLHL40	*MYPN*	

- *ACTA1* and *NEB*: >80% of all nemaline myopathies

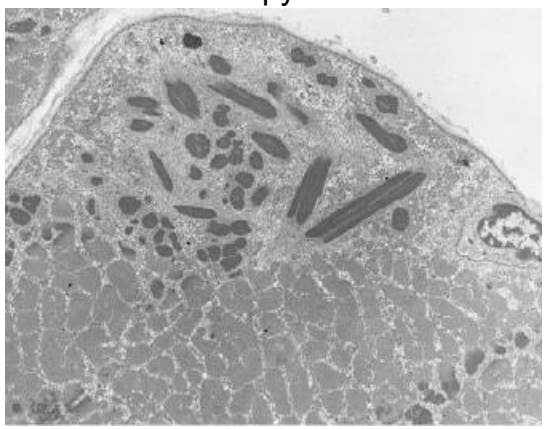
Histological features[2,3]

- Presence of rod-like structures called nemaline bodies
  - Stain red in the modified Gomori trichrome technique
  - Electron-dense structures visible by electron microscopy

Gomori trichrome staining[2]



Electron microscopy[2]



Figures from Claeys 2020. Used with permission from John Willey and Sons.

1. Cassandrini D, et al. *Ital J Pediatr*. 2017;43(1):101. 2. Claeys KG. *Dev Med Child Neurol*. 2020;62(3):297-302. 3. Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225.

NEB-Related Myopathy

Pathophysiology and genetics

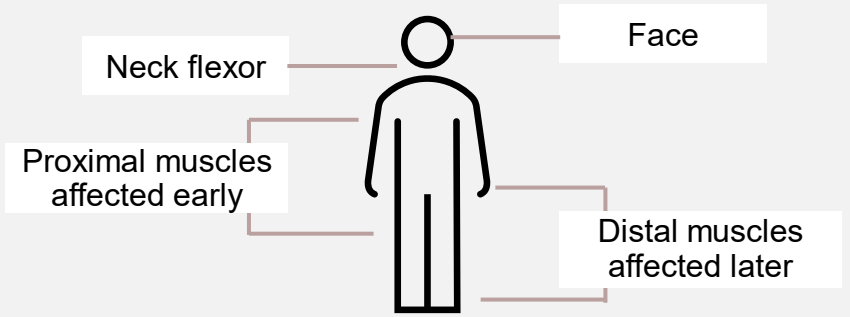
- *NEB* encodes nebulin, a large protein (600-900 kDa) fundamental to sarcomere structure
  - Connects the thin filament and the intermyofibrillar network
- Most cases are due to AR mutations

Clinical spectrum

- Wide phenotypic differences
  - Severe fetal akinesia syndrome
  - Neonatal-to-infantile onset
  - Adult-onset myopathy
- Over half of *NEB*-related nemaline myopathy cases show neonatal-to-infantile onset

Clinical presentation

Muscle weakness



- Respiratory involvement is common
- Cardiomyopathy is rare

AR, autosomal recessive.

Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225.

ACTA-Related Myopathy

Pathophysiology and genetics

- *ACTA1* encodes the skeletal muscle alpha-actin-1, the main actin isoform in adult skeletal muscles
- 90% of cases are AD and 10% are AR

Clinical spectrum

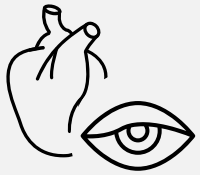
- One-third to half of patients have a severe phenotype, with death occurring before 1 year of age
- About one-third show typical perinatal onset

Clinical presentation

MRI findings

- Gluteus maximus
- Sartorius
- Adductor magnus
- Tibialis anterior

- More gastrointestinal complications than for patients with *NEB*-related myopathy
- Require gastrostomy/jejunostomy and feeding support



Not common

- Cardiac involvement
- Ptosis
- Ophthalmoplegia

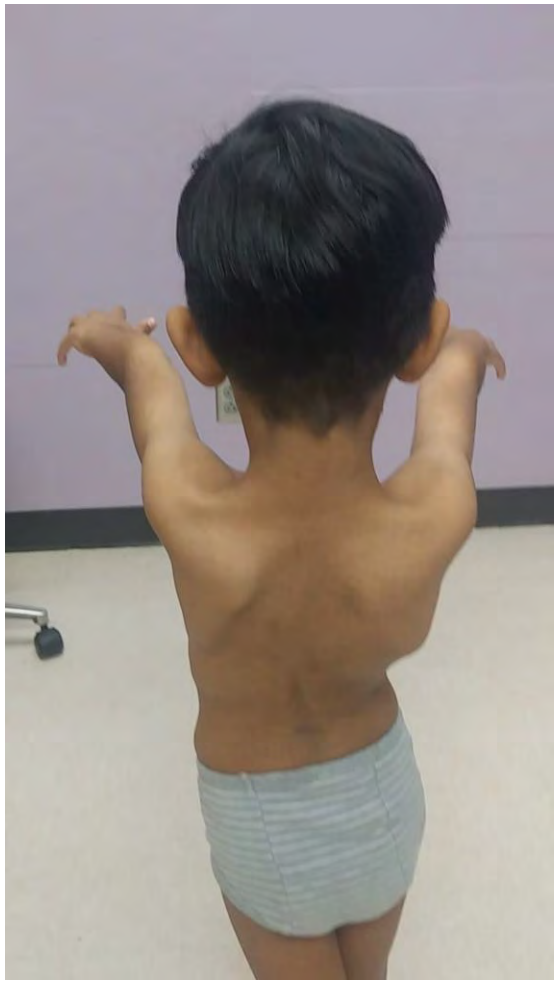
AD, autosomal dominant; AR, autosomal recessive; MRI, magnetic resonance imaging.

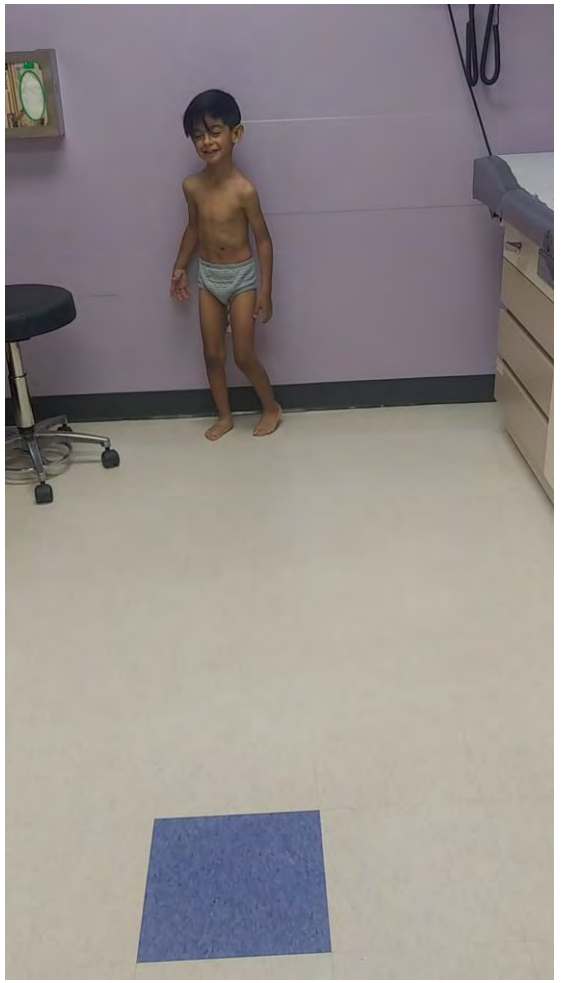
Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225.

KLHL40-Related Myopathy

5-year-old boy presenting with *KLHL40*-related myopathy

- Presented with hypotonia at birth
- Motor delays throughout childhood
- Feeding difficulties requiring a G-tube





Videos courtesy of Drs Gonzalez, Batley, and Iannaccone.

Core Myopathies

Genetic etiology

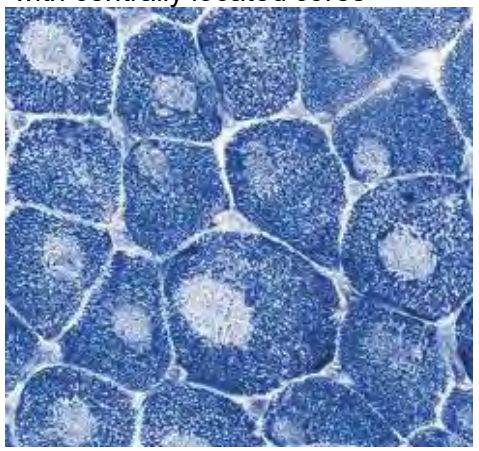
- 15 known causative genes

RYR1 (AD, AR)	*NEB*
SELENON	*ACTA1*
MYH7	*CCDC78*
TTN	*UNC45B*
ACTN2	*CFL2*
MEGF10	*TRIP4*
MYH2	*TNNT1*
	KBTBD13

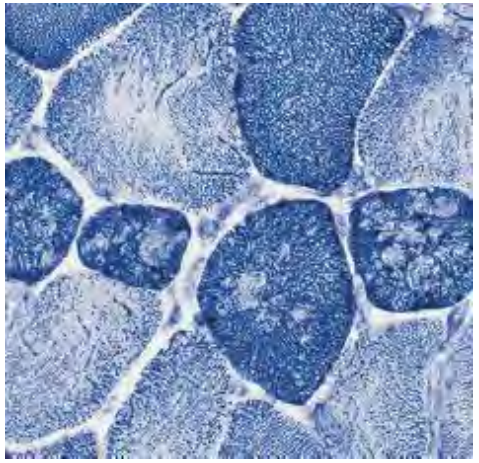
Pathology

- Lack of oxidative enzymes (eg, NADH) in localized regions of muscle fibers
- Central core
  - Commonly *RYR1*
- Minicore
- Multiminicore
  - Multiple cores with focal sarcomere disturbance
  - Commonly *SELENON*

NADH-TR staining shows fibers with centrally located cores



NADH staining shows fibers with multiminicores



Figures from Ogasawara 2023. Used with permission from Springer Nature.

AD, autosomal dominant; AR, autosomal recessive.

Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225.

RYR1-Related Myopathy

Pathophysiology and genetics

- *RYR1* encodes the ryanodine receptor isoform-1
  - Facilitates the release of calcium from the sarcoplasmic reticulum to the cytosol
- Most common congenital myopathy

Clinical spectrum

- Recessive mutations show a more severe phenotype than dominant mutations
- Multiple pathological phenotypes
  - CCD, MmD, malignant hyperthermia, CFTD, centronuclear myopathy, core-rod myopathy, dusty core myopathy, CNMDU1
- Risk of malignant hyperthermia

Clinical presentation

MRI findings: Involvement of the sartorius, adductor magnus, and soleus muscles
- Rectus femoris, gracilis, adductor longus, and tibialis anterior muscles are relatively spared

- Slow progressive weakness of the trunk and proximal muscles

- Common musculoskeletal issues in patients with CCD include hip dislocation, scoliosis, and joint contractures

CCD, central core disease; CFTD, congenital fiber-type disproportion; CNMDU1, congenital neuromuscular disease with uniform type 1 fiber; MmD, multiminicore disease; MRI, magnetic resonance imaging.

Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225.

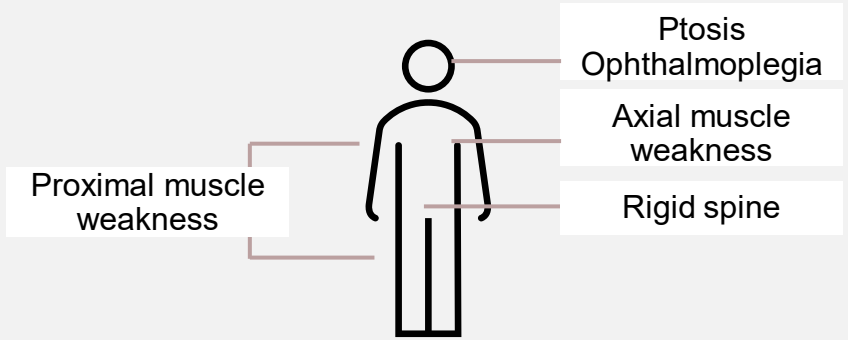
SELENON-Related Myopathy

Pathophysiology and genetics[1,2]

- *SELENON* encodes selenoprotein N, involved in:
  - Endoplasmic reticulum oxidoreduction
  - Calcium homeostasis
- *Bi-allelic null SELENON* mutations are significantly associated with more severe disease phenotypes

Clinical presentation[1,2]

Onset: Neonatal period to early childhood



- Respiratory failure is common around 10 years of age (>80%)

1. Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225. 2. Villar-Quiles RN, et al. *Neurology*. 2020;95(11):e1512-e1527.

Myotubular/Centronuclear Myopathies

Genetic etiology

- Centronuclear myopathy
  DNM2
  BIN1
  TTN
  RYR1
  SPEG
- X-linked myotubular myopathy
  MTM1

Pathology

- Muscle fibers resemble fetal myotubes
- Numerous fibers with large and centrally located nuclei
- Centronuclear myopathy
  - Milder phenotype with childhood or late-onset disease

Fibers with centrally located nuclei in muscle biopsy (H&E staining)

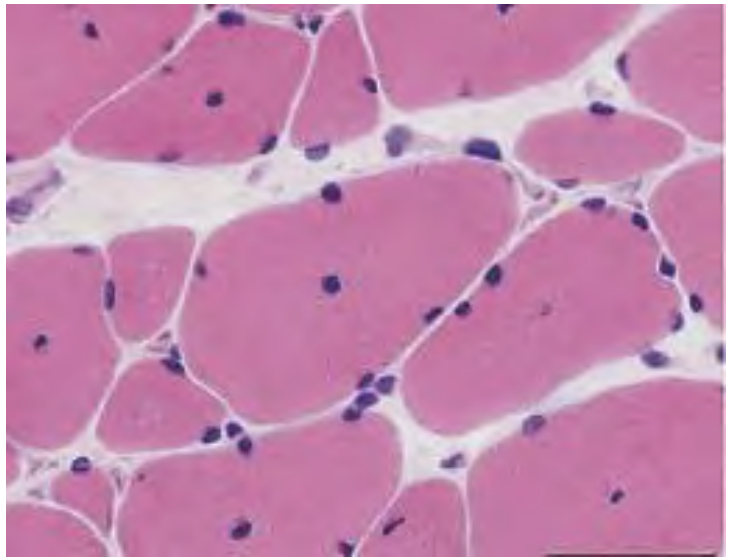


Figure from Ogasawara 2023. Used with permission from Springer Nature.

H&E, hematoxylin and eosin.

Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225.

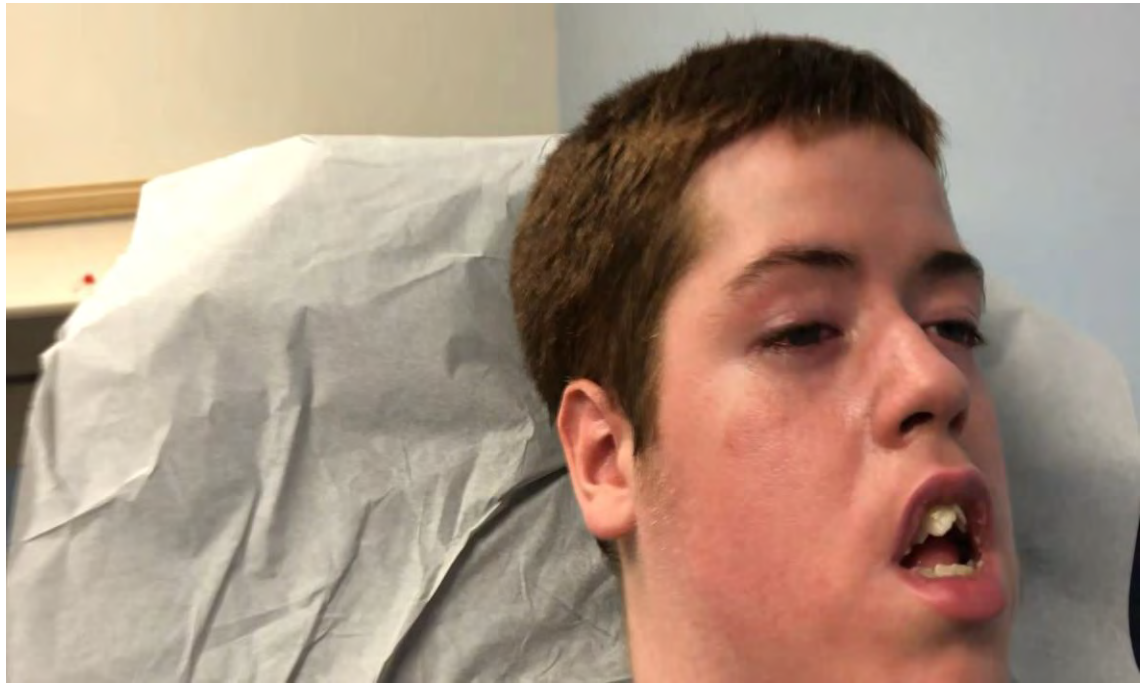
Myotubular/Centronuclear Myopathies (cont.)

Pathophysiology and genetics

- X-linked myotubular myopathy
  - Caused by *MTM1* gene encoding for myotubularin (MTM1) proteins
  - MTM1 is a ubiquitous peripheral membrane enzyme regulating the endosomal-lysosomal pathway and membrane trafficking

Clinical presentation

- Neonatal onset with severe phenotype
  - Profound, diffuse weakness and hypotonia
  - Severe respiratory failure and feeding trouble
  - Ophthalmoplegia and ptosis



Video courtesy of Drs Batley, Gonzalez, and Iannaccone.

Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225.

Congenital Fiber-Type Disproportion

Genetic etiology[1]

- 8 causative genes

  ACTA1
  SELENON
  TPM2
  TPM3
  RYR1
  TTN
  MYH7
  HACD1

Pathology[1,2]

- Disproportionate difference in fiber caliber between the type 1 (slow) and type 2 (fast) fibers
  - >25%-40% of type 1 fibers are smaller than 2A/2B
- Most affected children present with hypotonia and mild-to-severe generalized muscle weakness at birth or within the first year of life[2]

H&E staining showing moderate type 1 fiber atrophy

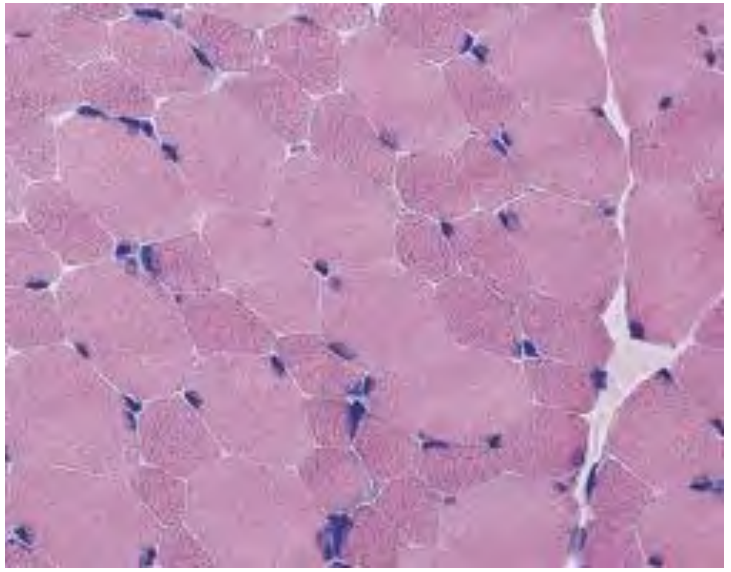


Figure from Ogasawara 2023. Used with permission from Springer Nature.

H&E, hematoxylin and eosin.

1. Ogasawara M, Nishino I. *J Hum Genet*. 2023;68(3):215-225. 2. Cassandrini D, et al. *Ital J Pediatr*. 2017;43(1):101.

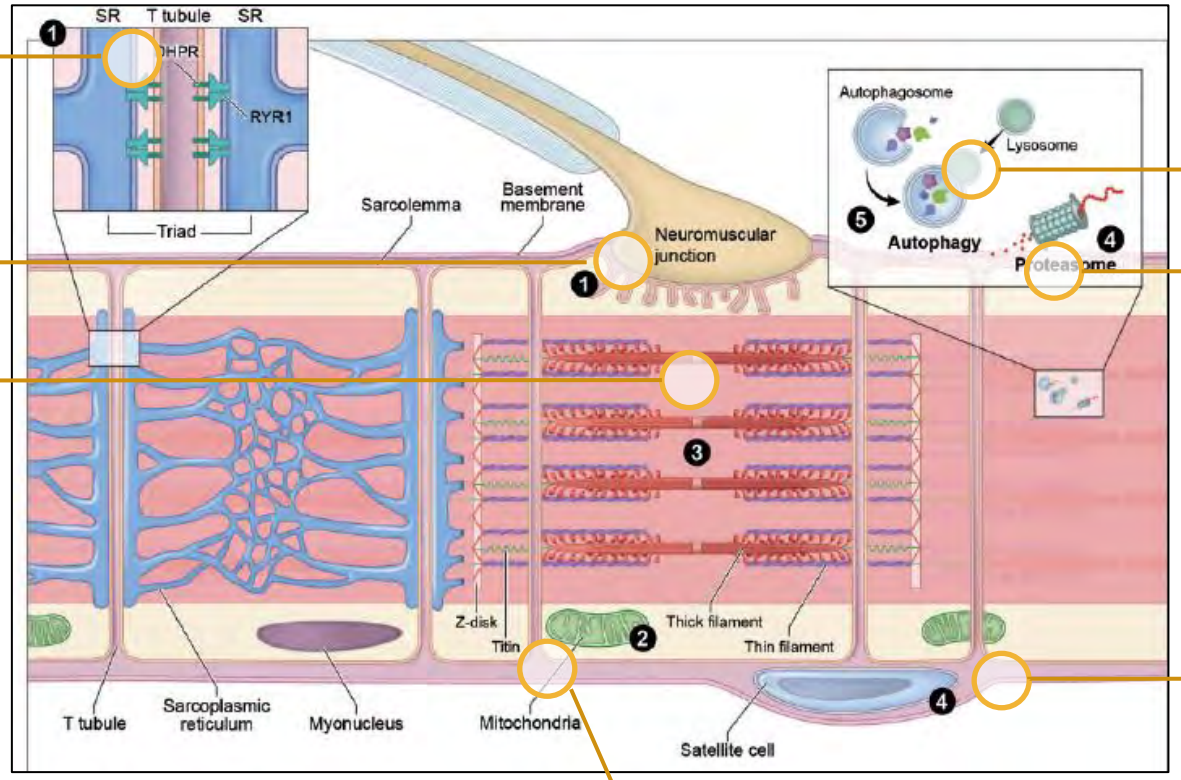
Pathophysiology

Muscle cell structures and pathways affected in congenital myopathies

Changes in sarcolemma and intracellular membrane remodeling

Impaired excitation-contraction coupling

Defects in myofibrillar force generation



Altered autophagy

Myofiber atrophy

Abnormalities in mitochondrial distribution and function

Figure from Ravenscroft 2015. Public Domain.

Ravenscroft G, et al. *Brain*. 2015;138(Pt 2):246-268.

Diagnosis

Diagnosis is based on characteristic weakness, confirmed through imaging and biopsy[1]

Serum CK, EMG, and NCS are usually normal and help rule out differential diagnosis[1,2]

Clinical evaluation[1,2]

- Family history
- General observation (eg, facial weakness in infant, hypotonia, ophthalmoparesis)

Imaging[1,3]

- Muscle ultrasound
- Muscle MRI
- Pattern recognition

Muscle biopsy[1]

- Specific for congenital myopathies
- Overlap between different subtypes

Serum CK[1,2]

- Normal or mildly elevated

EMG/NCS[1,2]

- EMG normal or myopathic
- NCS normal

Genetic testing to be used in combination with other tools[1,2]

CK, creatine kinase; EMG, electromyography; MRI, magnetic resonance imaging; NCS, nerve conduction studies.

1. North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116. 2. Cassandrini D, et al. *Ital J Pediatr*. 2017;43(1):101. 3. Carlier RY, Quijano-Roy S. *Semin Pediatr Neurol*. 2019;29:30-43.

Diagnosis – Muscle Imaging Patterns

Muscle imaging patterns can guide genetic testing decision

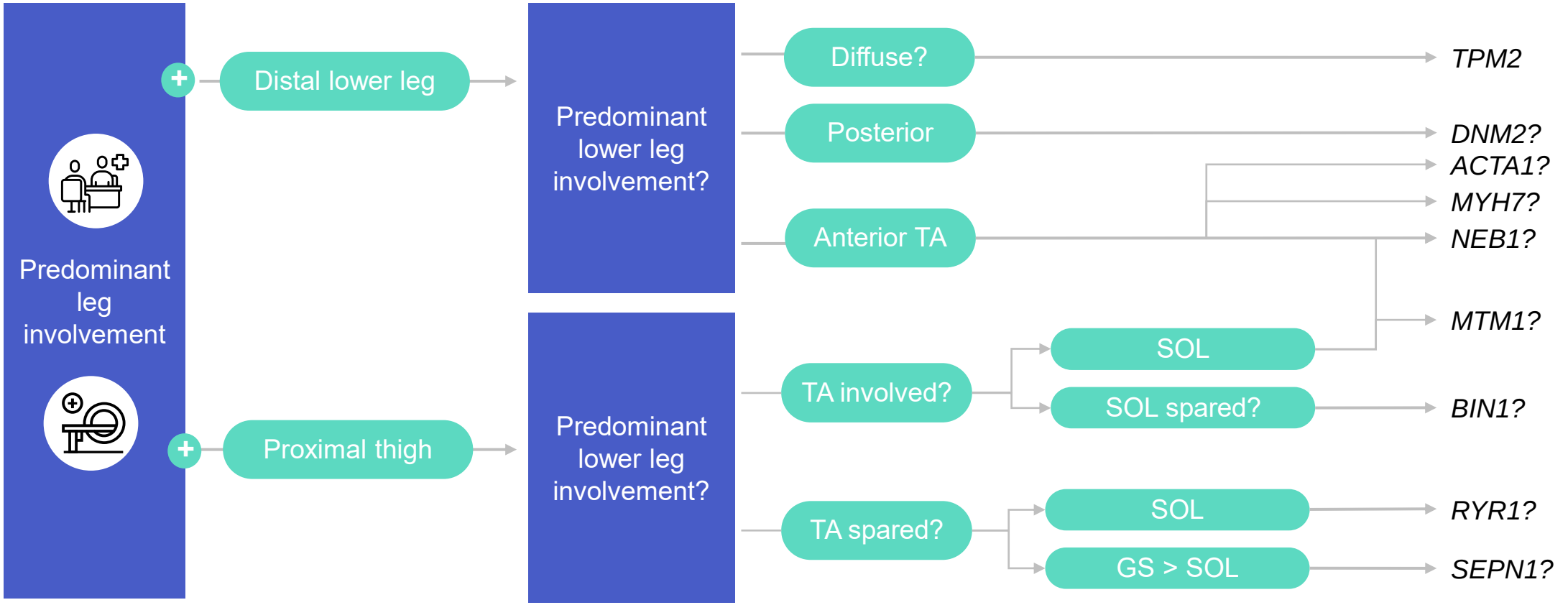


Figure from Quijano-Roy 2011 (Figure 10). Adapted with permission from Elsevier.

GS, medial/lateral gastrocnemius; SOL, soleus; TA, tibial anterior.
Quijano-Roy S, et al. *Semin Pediatr Neurol*. 2011;18(4):221-229.

Diagnosis – Muscle Imaging Patterns (cont.)

Muscle imaging of patients with mutations in the *RYR1* gene

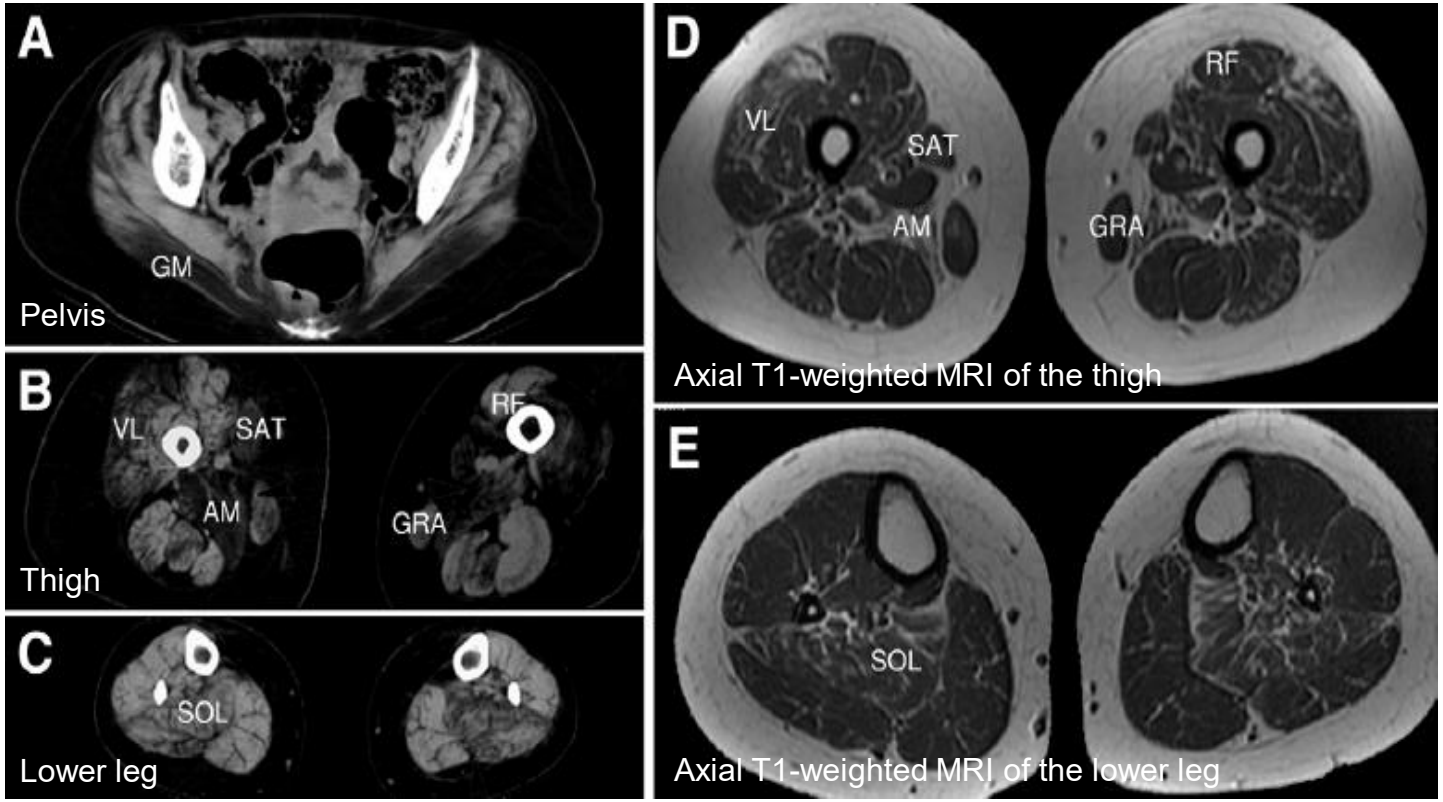


Figure from Quijano-Roy 2011. Used with permission from Elsevier.

In *RYR1*-related myopathy, the anterior compartment is involved, including the following muscles

- Pelvis: Gluteus maximus
- Thigh: Adductor magnus, vastus lateralis, vastus intermedius, semitendinosus, and sartorius
- Lower leg: Soleus and peroneal muscles

AM, adductor magnus; GM, gluteus maximus; GRA, gracilis muscle; MRI, magnetic resonance imaging; RF, rectus femoris; SAT, sartorius; SOL, soleus; VL, vastus lateralis.

Quijano-Roy S, et al. *Semin Pediatr Neurol*. 2011;18(4):221-229.

Diagnosis – Muscle Imaging Patterns (cont.)

Muscle imaging of patients with mutations in the *SEPN1* gene

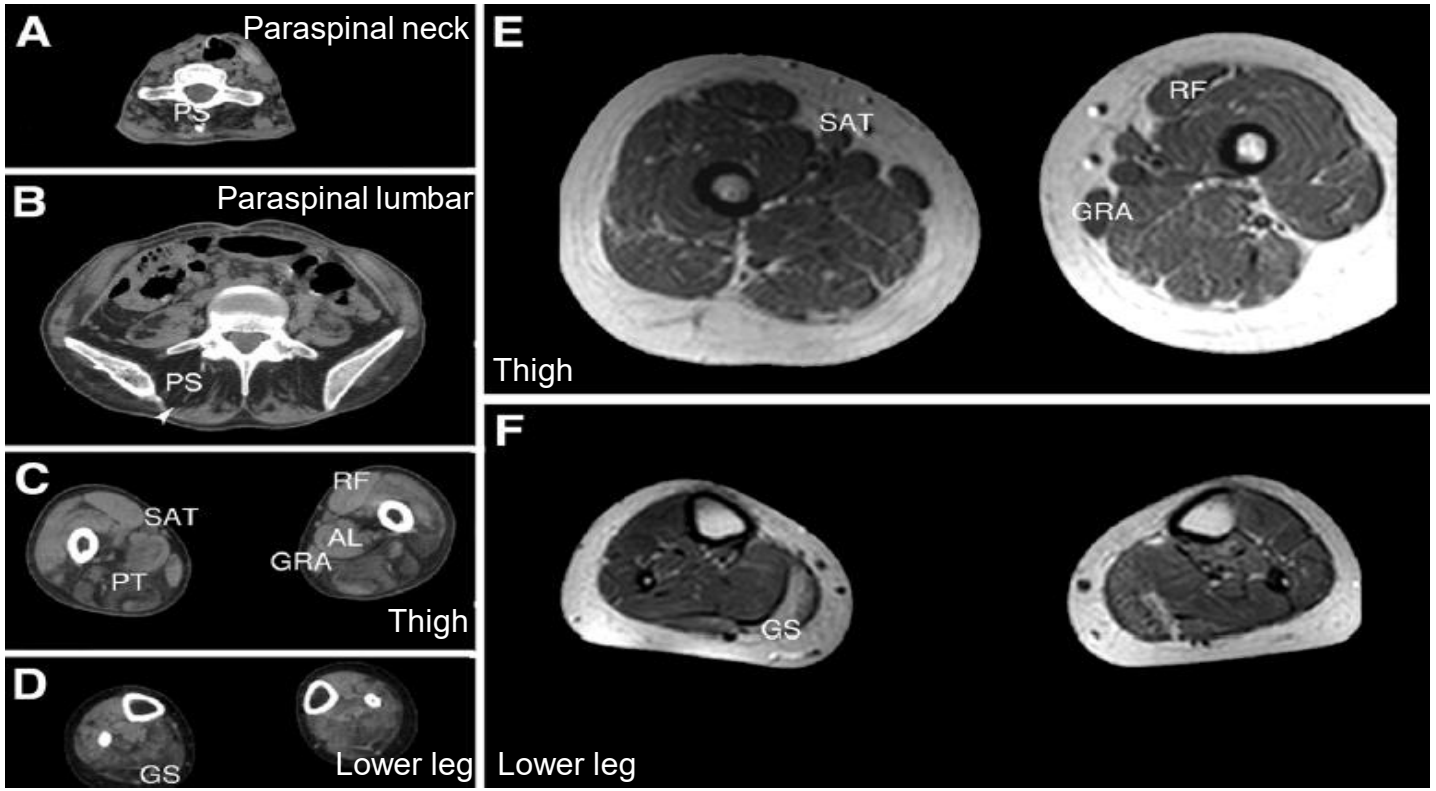


Figure from Quijano-Roy 2011. Used with permission from Elsevier.

In *SEPN1*-related myopathy, the posterior compartment is involved, including

- Neck: Severe hypotrophy of the sternocleidomastoid muscle
- Marked fatty degeneration in paraspinal, intercostal, and gluteal muscles
- Thigh: Sartorius and hamstring muscles are affected
- Lower leg: Medial and lateral gastrocnemius are affected

AL, adductor longus; GRA, gracilis muscle; GS, medial and lateral gastrocnemius muscles; PS, paraspinal cervical; PT, posterior thigh; RF, rectus femoris; SAT, sartorius.

Quijano-Roy S, et al. *Semin Pediatr Neurol*. 2011;18(4):221-229.

Differential Diagnosis

Other possible diagnosis[1,2]

There is significant clinical overlap with other neuromuscular disorders, including

- Congenital muscular dystrophies
- Congenital myotonic dystrophy
- Congenital myasthenic syndromes
- Metabolic myopathies – Pompe disease
- Spinal muscular atrophy
- Moebius syndrome
- Prader-Willi syndrome

When to suspect an alternate diagnosis[1,2]

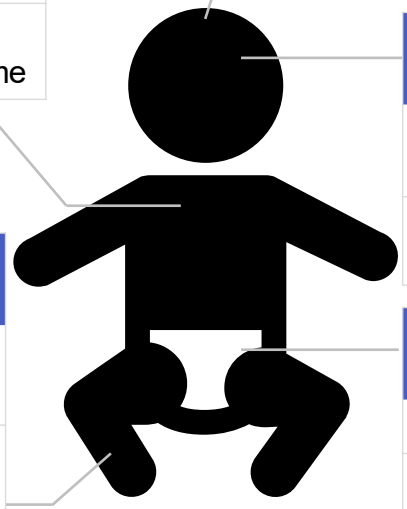
- Upper motor neuron signs
- Central nervous system abnormalities
- Tongue fasciculations
- Extreme joint laxity
- Metabolic abnormalities
- Creatine kinase 5 times over upper normal value

1. Claeys KG. *Dev Med Child Neurol*. 2020;62(3):297-302. 2. North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116.

Clinical Clues for Specific Myopathies: Newborn and Infant

Clinical features	Congenital myopathy	Differential diagnosis
Severe respiratory involvement at birth	NM, CNM (*MTM1*), severe *RYR1*	DM1, SMA 0, CMS, Pompe disease
Predominant axial hypotonia	*RYR1, SEPN1*	LMNA
Severe congenital hypotonia	NM, *MTM1*, *RYR1*	DM1, PWS, Down syndrome

Clinical features	Congenital myopathy	Differential diagnosis
Facial weakness	NM, CNM (*MTM1, RYR1, DNM2*)	DM1, CMS (rapsyn)
Facial dysmorphism (long face, dolichocephaly, high arched palate)	NM, CNM (*MTM1*, severe *DNM2*), severe RYR1	DM1
Bulbar weakness (sucking/swallowing)	NM, CNM (*MTM1*), severe *RYR1*	CMS, DM1, PWS, SMA



Clinical features	Congenital myopathy	Differential diagnosis
Ophthalmoplegia	CNM (*MTM1, RYR1, DNM2*), MmD (*RYR1*)	CMS, mitochondrial
Ptosis	CNM (*MTM1, RYR1, DNM2*), MmD, CCD	CMS, DM1

Clinical features	Congenital myopathy	Differential diagnosis
Orthopedic deformities	*RYR1*, NM	COL6, CMS
Club feet	NM, *RYR1*	CMS, DM1, CHS

Clinical features	Congenital myopathy	Differential diagnosis
Hip dislocation	RYR1	COL6
Fetal akinesia/ severe arthrogryposis	NM (*ACTA1, NEB*), severe *RYR1, KLHL40*	CMS, SMA 0, CHS

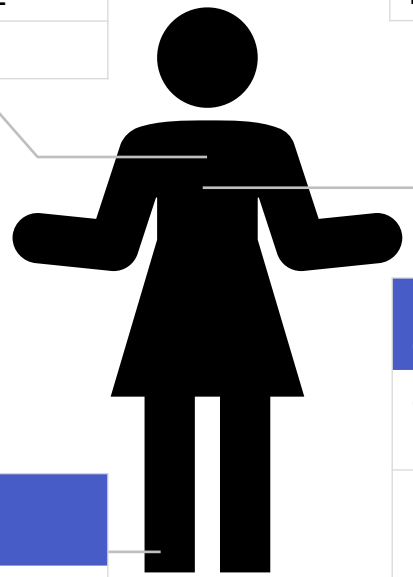
CCD, central core disease; CHS, central hypoventilation syndrome; CMS, congenital myasthenic syndrome; CNM, centronuclear myopathy; COL6, Ullrich congenital muscular dystrophy; DM1, myotonic dystrophy type 1; MmD, multiminicore disease; NM, nemaline myopathy; PWS, Prader-Willi syndrome; SMA, spinal muscular atrophy.

North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116.

Clinical Clues for Specific Myopathies: Older Children

Clinical features	Congenital myopathy	Differential diagnosis
Scoliosis	*SEPN1, RYR1*, NM	COL6, LAMA2
Rigid spine	*SEPN1*, *RYR1*	

Clinical features	Congenital myopathy
Malignant hyperthermia	CCD, MmD, CNM (*RYR1* only)



Clinical features	Congenital myopathy	Differential diagnosis
Cardiomyopathy	*TTN, MYH7*, rarely *ACTA1*	Pompe disease
Respiratory involvement and axial involvement out of proportion to skeletal muscle weakness	*SEPN1*, NM (*NEB, TPM3, ACTA1*)	LMNA, CMS, Pompe disease

Clinical features	Congenital myopathy	Differential diagnosis
Foot drop/ pes cavus	NM (*NEB, TPM3, TPM2*), *DNM2*, *MYH7*	Peripheral neuropathy

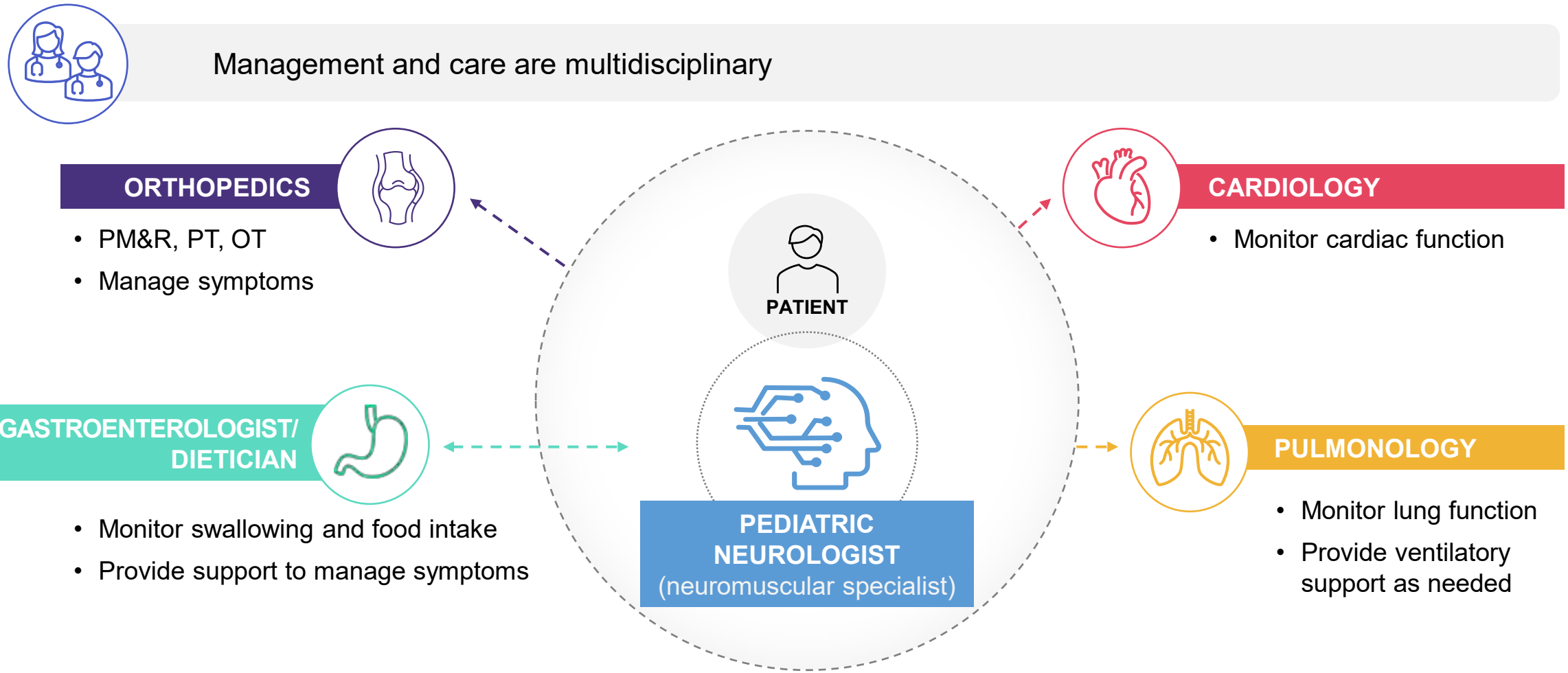
Tables adapted from North 2014 (Table 1). Open Access. (CC-BY-NC-ND)

CCD, central core disease; CMS, congenital myasthenic syndrome; CNM, centronuclear myopathy; COL6, Ullrich congenital muscular dystrophy; MmD, multiminicore disease; NM, nemaline myopathy.

North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116.

Standard of Care Guidelines

Management and care are multidisciplinary



OT, occupational therapy; PM&R, physical medicine and rehabilitation; PT, physical therapy.

Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Standard of Care Guidelines: Neurology

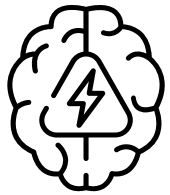
Neurological care

- Coordinate care with other specialists
- Monitor for respiratory, speech, and swallowing difficulties
- Mental health care
- Pain management

Follow-up

- Age <12 months: Every 3-4 months
- Older children: Every 6-12 months

Central nervous system



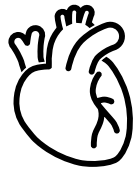
Central nervous system is rarely involved

- Patients who experience severe respiratory failure at birth may experience hypoxic-ischemic encephalopathy
- Mild cognitive impairment: Reported in patients with centronuclear myopathy (*DNM2* gene mutation)

Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Standard of Care Guidelines: Cardiology

Cardiological care

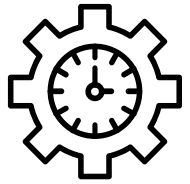


Cardiac involvement

- Primary cardiomyopathy is rare
- Reported rarely in patients with *ACTA1*, *DNM2*, and *TPM2* mutations
- Risk of cardiac involvement is higher in patients with cor pulmonale (*MTM1* or *RYR1* mutations)

Follow-up

- Recommendation is screening in asymptomatic patients every 2 years



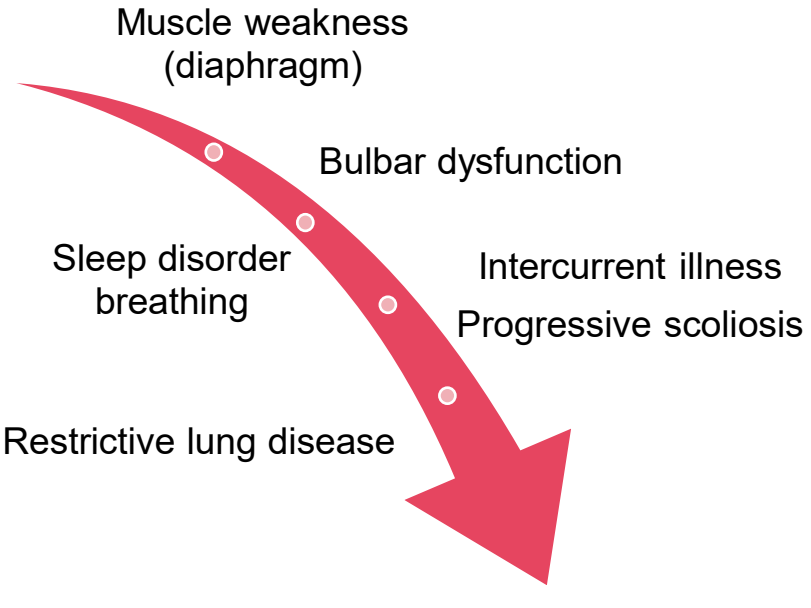
Management

- Frequent evaluation based on overt symptoms or echocardiographic abnormalities

Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Standard of Care Guidelines: Respiratory

Systems affecting respiratory function



All patients with congenital myopathy should be considered at risk for respiratory insufficiency

Severe respiratory involvement seen in congenital myopathies with mutations in *MTM1*, *SEPN1*, *DNM2*, *NEB*, *TPM3*, and *ACTA1* genes

- Patients with X-linked myotubular myopathy (*MTM1* mutations) and severe nemaline myopathy (*ACTA1*) require ventilatory support from birth

Wang CH, et al. *J Child Neurol.* 2012;27(3):363-382.

Standard of Care Guidelines: Respiratory (cont.)

Pulmonary function tests

	Every 6-12 months	Annually	Every 1-2 years, when stable
Highly recommended	• Sitting spirometry* • Maximal inspiratory pressure, maximal expiratory pressure • Peak cough flow	• Overnight oximetry with measurement of CO_2 (CBG, transcutaneous CO_2, end-tidal CO_2)	• N/A
Recommended	• Supine spirometry • Oximetry spot check and/or venous bicarbonate	• Comprehensive pulmonary function tests, including lung volumes	• Attended polysomnography

*Spirometry is indicated for children older than 5 years of age.
CBG, capillary blood gas; N/A, not applicable.
Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Standard of Care Guidelines: Respiratory (cont.)

Respiratory maintenance treatments

Anticipatory care

- Adapted to patient-specific phenotype
- Vaccinations (influenza, COVID-19, pneumococcal)
- Mechanical or manual assisted cough
- Airway clearance techniques
- Noninvasive ventilatory support (BiPAP)
- Invasive ventilation in certain cases

Acute respiratory illness care

- Secretion clearance (cough assist as often as needed)
- Prophylactic antibiotics sometimes considered
- Avoid oxygen alone
- May require increased used of BiPAP

BiPAP, bilevel positive airway pressure.

Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Standard of Care Guidelines: Orthopedics and Rehab

Recommendations

- Orthopedic complications like congenital hip dislocation and scoliosis are more prominent in patients with *RYR1*- and *SEPN1*-related myopathies, respectively
- Recommendations are to maximize function and independence
  - Promotion of physical activity
- Endurance exercises 2-3x/week
- Prevention and correction of deformities
  - Various Therapies
- Bone health
- Pain management

General management

- Exercise
- Maintain ability to stand (orthotics, standing frames) to assist in contracture management and improve bone health
  - Contracture management through stretching and orthotics
  - Caution with using standing frames for patients with severe contractures or osteopenia (risk for metaphyseal fractures)
- Promote assisted ambulation to maintain independent mobility
  - Power wheelchairs and adaptive vehicles with safety devices
  - Consider environmental modifications, school accommodations and support
- Maintain joint range of motion with passive- and active-assisted stretching, splints, and serial casting
  - Botulinum toxin is contraindicated

Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Standard of Care Guidelines: Orthopedics and Rehab (cont.)

Scoliosis management

Observation

- Spinal examination by clinical observation at every visit
- Spine X-ray at detection and monitor every 6 months (nonambulatory patients) or annually (ambulatory patients)

Management

- Orthoses: For curves between 20 and 40 degrees
- Spinal surgery consideration: Curvature >50 degrees

Contractures and deformities

- Preventive measures like ankle and/or foot orthoses and knee immobilizers are preferred
  - Knee contractures: Surgery is rarely indicated
  - Serial casting and heel cord lengthening can be indicated for foot deformities

Congenital hip subluxation/dislocation

- Common condition in patients with central core myopathy (*RYR1*-related myopathy)
- Flexion–abduction splinting (Pavlik harness) is common treatment in the early postnatal period
- No consensus in management if asymptomatic in nonambulatory children
- Hip dislocation surgery in ambulatory patients can worsen weakness and compromise ambulation

Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Standard of Care Guidelines: Orthopedics and Rehab (cont.)

Swallowing and nutrition management

- Infants: Growth monitoring (height and weight) at least every 3 months
- Video fluoroscopic swallow study recommended when swallowing problems are identified
  - Supplemental formulas
  - Consider using nasogastric tube and switching to gastronomy tube when child does not meet their caloric needs orally

GI motility management

- Management of gastroesophageal reflux and constipation is often required

Speech

- Referral to speech/language pathologist
- Consult for alternative and augmentative communication
- Oral surgeon and ear-nose-throat specialist can be involved

Oral care

- Referral to a pediatric dentist by 1 year of age
- Referral to an orthodontist for an assessment of malocclusion and/or a high arch palate should be made by age 6 or 8 years
- Surgical treatment of severe malocclusion may not be considered due to the high risk of serious complications from intubation and anesthesia

GI, gastrointestinal.

Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Specific Recommendations

Pregnancy

- Patients considered high risk
- Specific subtypes associated with diaphragmatic weakness are at higher risk
- Consider malignant hyperthermia risk

Bulbar weakness

- Marked in patients with
  - Nemaline myopathy (due to *NEB* mutations)
  - Multiminicore disease, subgroups of centronuclear myopathy
- Refer for speech, language, and feeding assessments

Malignant hyperthermia

- Pharmacogenetic disorder in which volatile anesthetics trigger a sustained release of calcium from the sarcoplasmic reticulum
  - Leads to muscle rigidity, hypermetabolism, rhabdomyolysis, and death
- Malignant hyperthermia is always a concern in patients with myopathy
  - High risk associated with *RYR1*-related myopathies
  - Avoid succinylcholine and inhalational agents (other than nitrous oxide)

Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382.

Therapeutic Approaches in the Pipeline

1. ClinicalTrials.gov. NCT03199469. Accessed July 4, 2024. https://clinicaltrials.gov/study/NCT03199469. 2. ClinicalTrials.gov. NCT04915846. Accessed July 4, 2024. https://clinicaltrials.gov/study/NCT04915846. 3. ClinicalTrials.gov. NCT04141670. Accessed July 4, 2024. https://clinicaltrials.gov/study/NCT04141670. 4 Gineste C et al. Curr Opin Pharmacol. 2023; 68:102328.

ASPIRO Study

Gene Transfer Clinical Study in X-Linked Myotubular Myopathy

- Phase 2/3, multinational, open-label, ascending-dose, delayed-treatment, concurrent control clinical study
- Evaluate safety and efficacy of AT132 in patients with X-linked myotubular myopathy
- AT132 is an AAV8-mediated gene therapy delivering human *MTM1*

- Male <5 years of age
- Diagnosed with an X-linked myotubular myopathy
- Genetically confirmed *MTM1* mutation
- Requires mechanical ventilation

10-year follow-up

Part 1
Dose escalation

Part 2*
Pivotal expansion cohort

Primary outcome measures at 24 and 48 weeks†
- Change from baseline in hours of ventilation

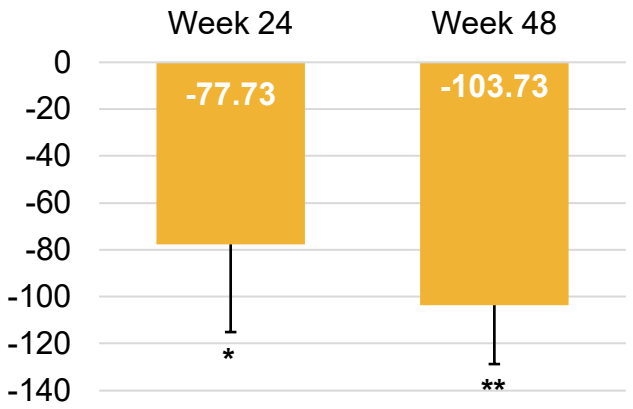
Secondary outcome measures up to 24 and 48 weeks†
- Independently sitting for at least 30 seconds
- Time to reduction in required ventilation
- Change from baseline in disease-specific measures
- Patient functioning, caregiver experience
- Survival
- Safety up to month 120

*Planned. Due to unexpected deaths, Part 2 was stopped and analyses were done on an as-treated basis. †Added as part of request from FDA to evaluate durability of effects.
ClinicalTrials.gov. NCT03199469. Accessed July 4, 2024. https://clinicaltrials.gov/study/NCT03199469.

Results From the ASPIRO Study

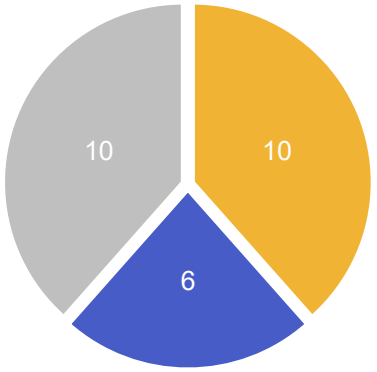
Improvements in ventilation

Estimated percentage point difference (95% CI) in reduction from baseline in ventilation hours per day between lower dose and control cohorts



*P=0.0002; **P<0.0001.

Ventilator independence was achieved by 16 dosed participants



- Achieved in high dose
- Achieved in low dose
- Not achieved

Safety

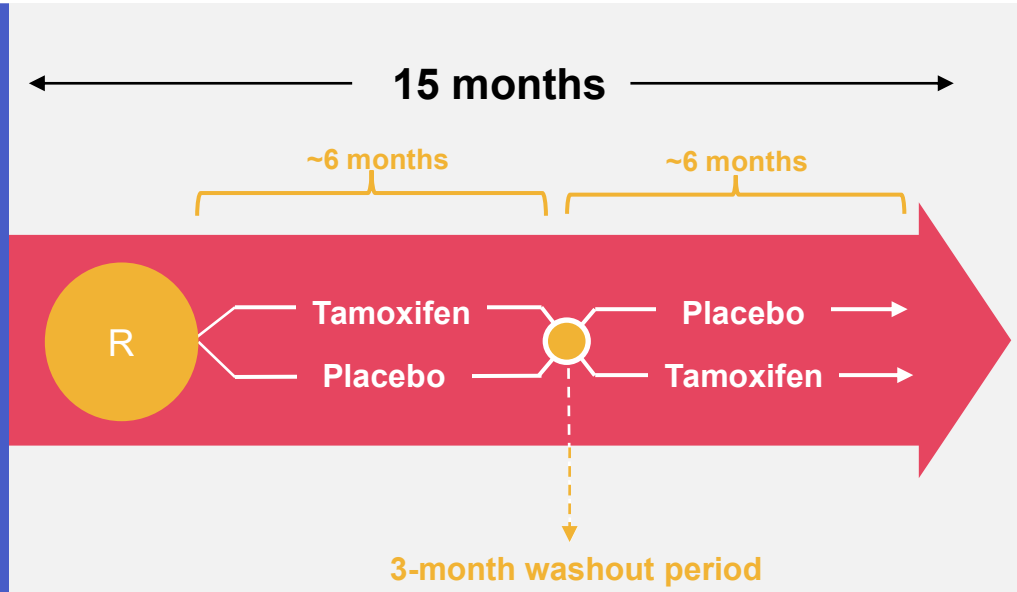
- Most patients in both the dosed and control groups had serious adverse events
  - Four deaths (1 in low dose, 3 in high dose) led to pause of the ASPIRO trial
    - All had cholestatic liver failure
    - Perhaps related to underlying liver disease in patients with *MTM1* mutation
  - Three deaths of causes similar to those observed in the natural history of the disease were reported in the control group

Shieh PB, et al. *Lancet Neurol.* 2023;22(12):1125-1139.

TAM4MTM Study: Tamoxifen Therapy for Myotubular Myopathy

- Phase 1/2, randomized, double-blind, single-crossover study
- Evaluate efficacy and safety of tamoxifen therapy in patients with X-linked myotubular myopathy
- Preclinical studies showed improved survival, motor function, and histopathological benefits

- Male ≥6 months of age
- Diagnosed with X-linked myotubular myopathy (*MTM1* mutation)



Primary outcome measures
- Change from baseline in MFM32, CHOP INTEND, 10-meter walk text velocity

Secondary outcome measures
- Change in pulmonary function test
- Time off invasive ventilation
- Adverse events
- Assessments of biomarker (microRNA 133a)

CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; MFM32, Motor Function Measure 32.
ClinicalTrials.gov. NCT04915846. Accessed July 4, 2024. https://clinicaltrials.gov/study/NCT04915846.

Nemaline Myopathy Natural History Study

- Multicenter, prospective, longitudinal cohort study
- To define disease natural history and clinical outcome measures to inform future clinical trials
- Seven sites across North America and Europe; results anticipated in 2028

- 0-18 years of age with *ACTA1*- or *NEB*-related nemaline myopathy
- Goal sample size: 50 patients (~25 *ACTA1* and ~25 *NEB*)

3-year follow-up

In-person assessments

Every 6 months (children >12 months old)

Every 3 months (infants <12 months old)

Outcome measures
- Medical assessments
- Age-appropriate and ambulatory-conscious clinical function scores
- Spirometry
- Ventilatory status
- Echocardiogram and electrocardiogram
- Serological markers

Site-specific outcome measures
- Wearables
- Actigraphy
- Lower extremity imaging

Piccoli C, et al. Poster. MDA Clinical & Scientific Conference. 2023 (#M231).

Resources

CMDIR congenital muscle disease international registry leading the way to a treatment and cure	https://www.cmdir.org/
International Family Registry for Centronuclear and Myotubular Myopathies	https://www.joshuafrase.org/get-involved/global-map.php
RYR-1 FOUNDATION	https://ryr1.org/
The Myotubular and Centronuclear Myopathy Patient Registry	https://mtmcnmregistry.org/