NICU Grand Rounds

Neonatal Neuromuscular

Carla Zingariello, DO
Assistant Professor Pediatrics
Division of Child Neurology
University of Florida

Talk Outline

- Part 1: Normal muscle development in the neonatal period
- Part 2: Approach to the Hypotonic Infant or "Floppy Baby"
    - Distinguishing between central and peripheral causes of low tone
    - The Neonatal Neuromuscular Exam
    - Diagnostic approach
- Part 3: Neuromuscular disorders presenting in the neonatal period
- Part 4: Cases

Learning Objectives

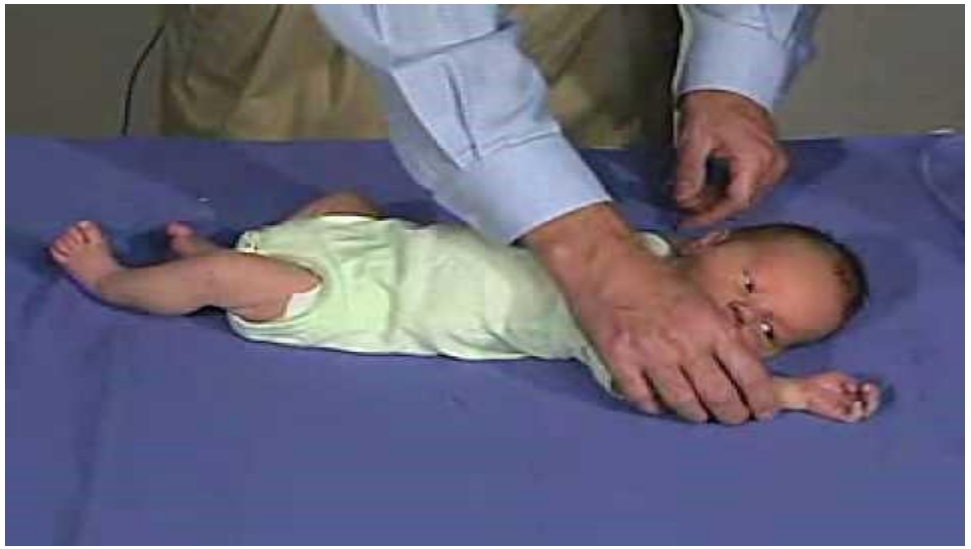
1. Define Hypotonia vs Weakness in a neonate
2. Differentiate and classify Central vs Peripheral hypotonia in a neonate
3. Describe treatments available for neonates with neuromuscular disorders

Part 1: Neuromuscular Development

Normal Neonatal Neuromuscular Development

- **Muscle tone**
  - 28 weeks GA: minimal resistance to passive manipulation of extremities
  - 32 weeks GA: flexor tone becomes apparent in the legs
  - 36 weeks GA: flexor tone prominent in the legs and noted in the arms
- **Muscle movements**
  - 28 weeks GA: movements tend to involve entire limb or trunk
  - 32 weeks GA: movements mainly flexor at hips and knees, often in unison
  - 36 weeks GA: legs stronger and alternating and arms flexor

Neonatal Tone



Part 2: Approach to the “Floppy Baby”

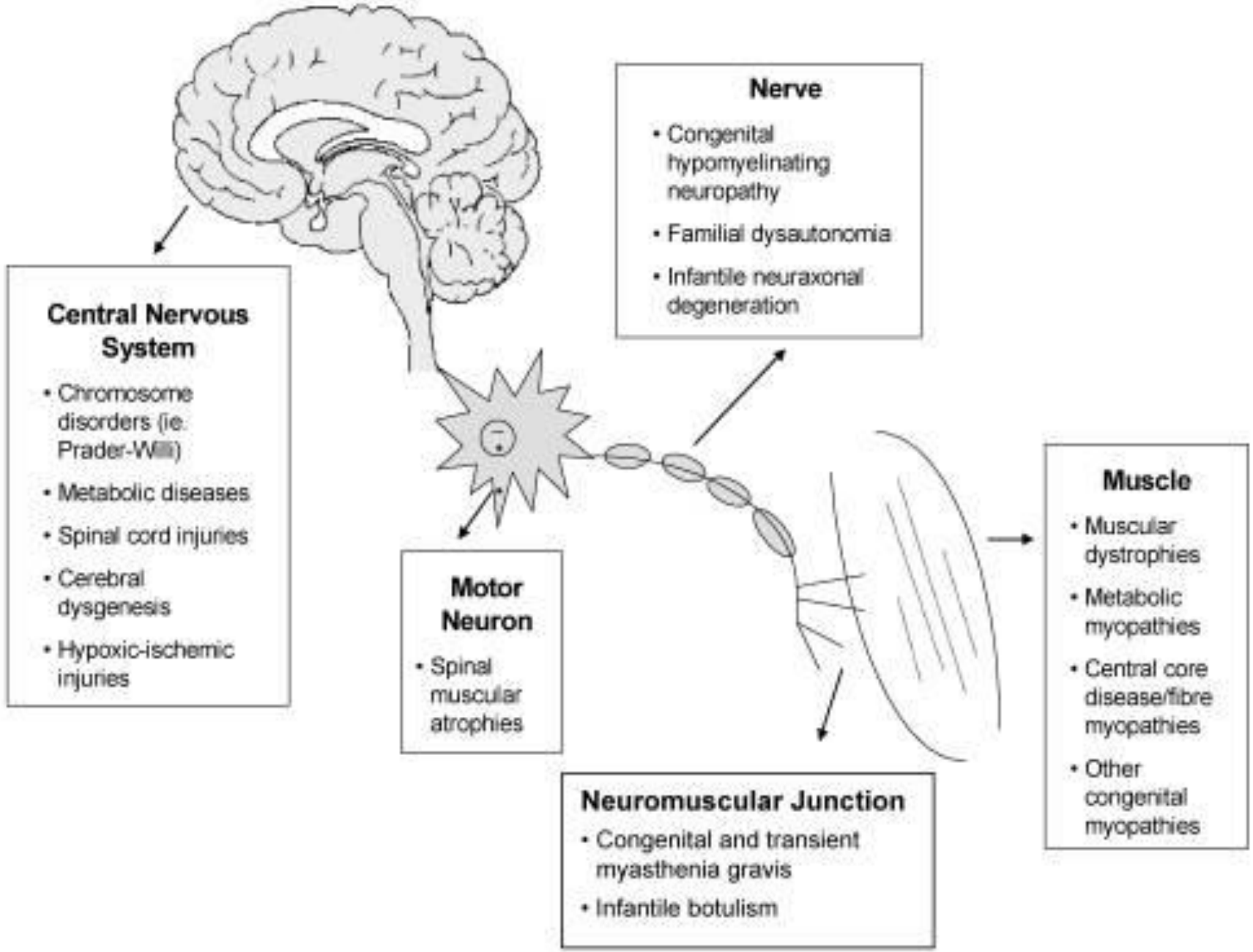
Hypotonia vs Weakness

- Hypotonia:
  - Appendicular: Reduced resistance to passive ROM in joints
  - Axial: Impaired ability to sustain postural control/anti-gravity movement
- Weakness:
  - Reduction in the maximum power that can be generated
- *Weak infants always have hypotonia, but hypotonia can exist without weakness

Central vs Peripheral Hypotonia

- **Central** (brain, spinal cord)
  - 60-80% of hypotonia cases
  - e.g. HIE, stroke, chromosomal disorders (Fragile X, Prader-Willi), congenital syndromes, metabolic disease

- **Peripheral** (motor neuron, nerve, NMJ, muscle):
  - e.g. SMA, congenital myotonic dystrophy, congenital muscular dystrophy, congenital myopathy, congenital myasthenic syndrome, Pompe disease, congenital neuropathy, botulism, brachial plexopathy


Central Nervous System
• Chromosome disorders (ie. Prader-Willi)
• Metabolic diseases
• Spinal cord injuries
• Cerebral dysgenesis
• Hypoxic-ischemic injuries
Nerve
• Congenital hypomyelinating neuropathy
• Familial dysautonomia
• Infantile neuraxonal degeneration
Motor Neuron
• Spinal muscular atrophies
Neuromuscular Junction
• Congenital and transient myasthenia gravis
• Infantile botulism
Muscle
• Muscular dystrophies
• Metabolic myopathies
• Central core disease/fibre myopathies
• Other congenital myopathies

Etiology of Neonatal Hypotonia

Summary of Diagnosis in Hypotonic Infants

Central hypotonia	**47 (79.66%)**
Hypoxic-ischemic	**2 (4.26)**
Other causes of encephalopathy	**2 (4.26)**
cerebral haemorrhage	**4 (8.51)**
Cerebral anomalies	**7 (14.89)**
Chromosomal abnormalities	**4 (8.51)**
Syndromic hypotonia*	**3 (6.38)**
Non syndromic hypotonia	**5 (10.64)**
Metabolic disorders**	**8 (17.2)**
Transient hypotonia	**12 (25.53)**
Peripheral hypotonia	**6 (10.17)**
Spinal Muscular Atrophy	**1 (16.7)**
Myopathy	**5 (83.3)**
Undiagnosed Hypotonia	**6 (10.17)**

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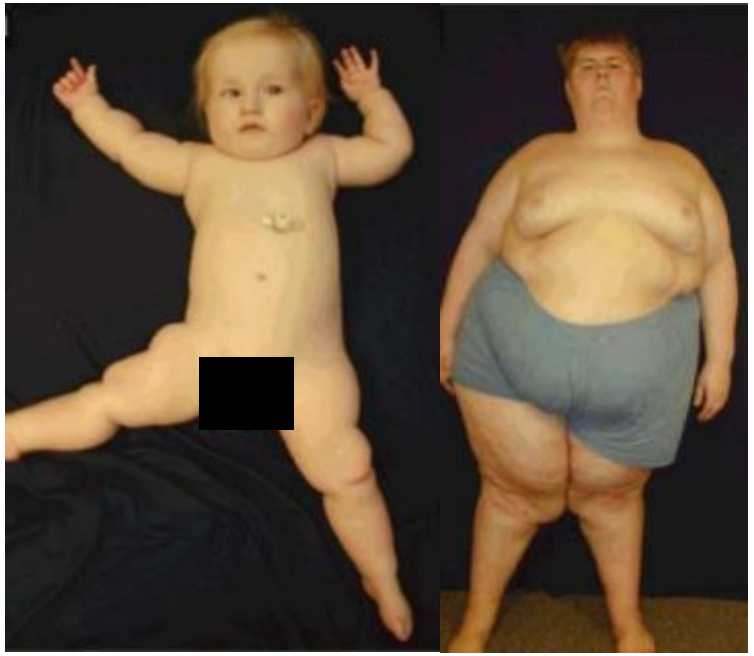
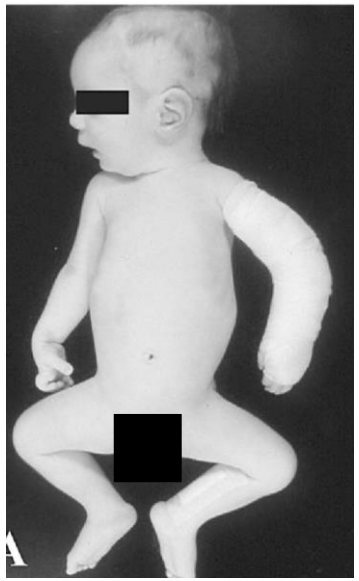
Central Hypotonia

Down Syndrome

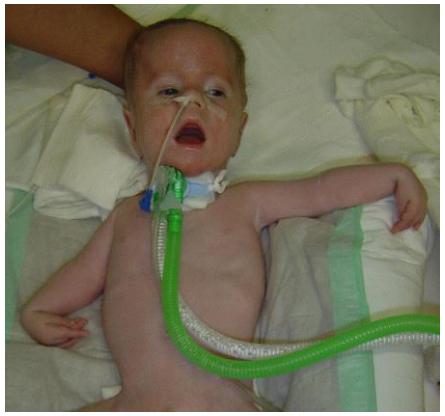


Prader-Willi Syndrome

Peripheral (Neuromuscular) Hypotonia

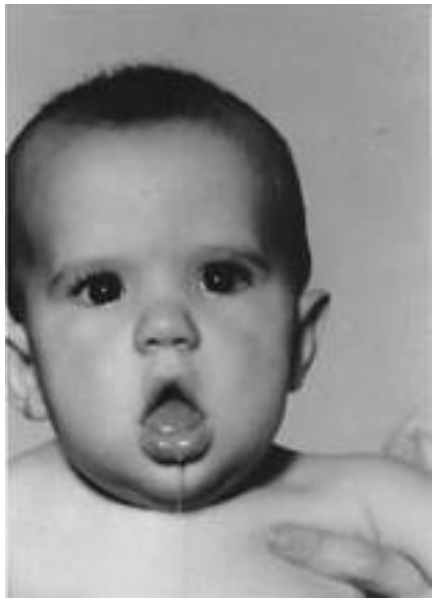


Type 0 SMA



Congenital myopathy

Congenital
Myasthenic Syndrome



Congenital Myotonic
Dystrophy

Neonatal Neuromuscular - History

- Prenatal/Perinatal History
  - Diminished fetal movements, polyhydramnios (3rd trimester)
- Neonatal History
  - Difficulty feeding, respiratory problems, arthrogryposis
- Family History
  - Neuromuscular disorders, early death in infancy, developmental delay, or maternal history of myotonia or Myasthenia Gravis

Examination	Central	Peripheral
Mental status	Abnormal: Seizures Encephalopathy	Normal
Cranial nerves	Localizing pattern e.g. facial nerve palsy	Localizing pattern e.g. facial nerve palsy Extraocular muscle involvement Bulbar weakness
Motor	Upper motor signs: Normal muscle bulk Spasticity Brisk reflexes Hemideficits	Lower motor signs: Reduced muscle bulk Hypotonia Decreased reflexes Weakness with different patterns
Sensory	Specific patterns: Hemisensory loss Sensory level/sweat level	Poor response diffusely

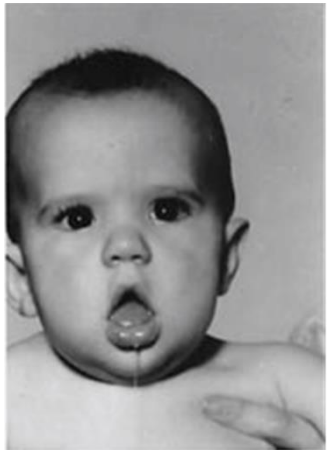
Exam Clues for Localization

Categories	Examination findings
Anterior horn	• Weak • High arched palate • Bell-shaped torso • Reduced muscle bulk • Absent reflexes • Fasciculations (especially tongue)
Neuropathy	• Weak • Absent reflexes • Fasciculations (rare) • Sensory deficits
Neuromuscular junction	• Weak • Fatigability • Muscle bulk normal • Extraocular, bulbar, respiratory muscle involvement
Muscle	• Weak • Reduced muscle bulk (patterns) • Pseudohypertrophy • Contractures • Proximal > distal (most cases) • Extraocular, bulbar, respiratory muscle involvement

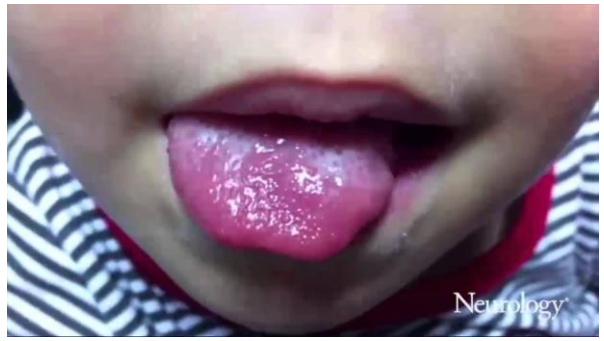
Cranial Nerves

Ptosis

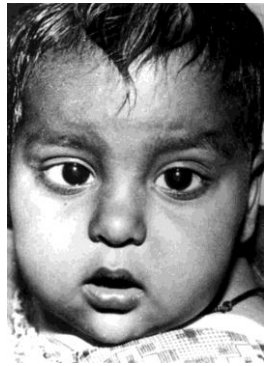
Facial weakness



Tongue fasciculations

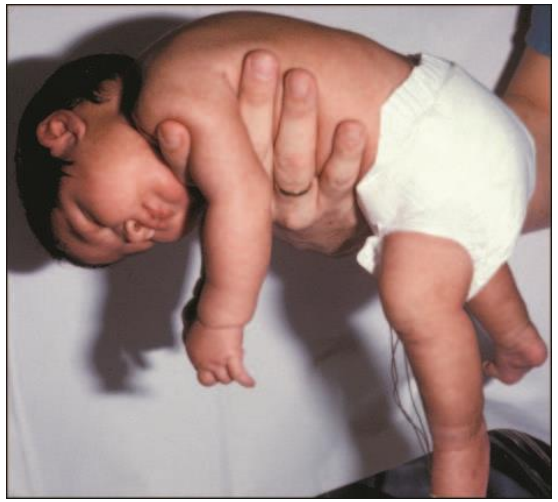


Ophthalmoparesis

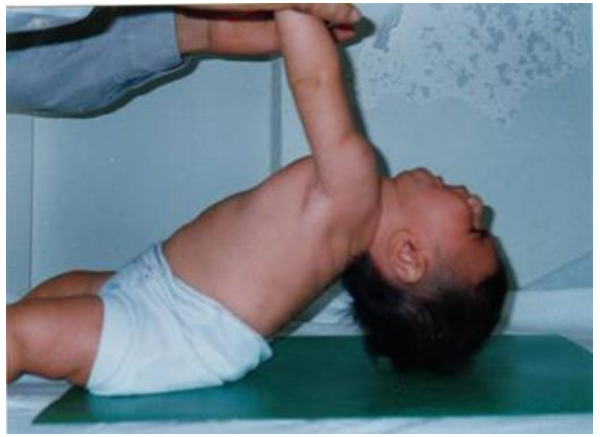


Axial Hypotonia

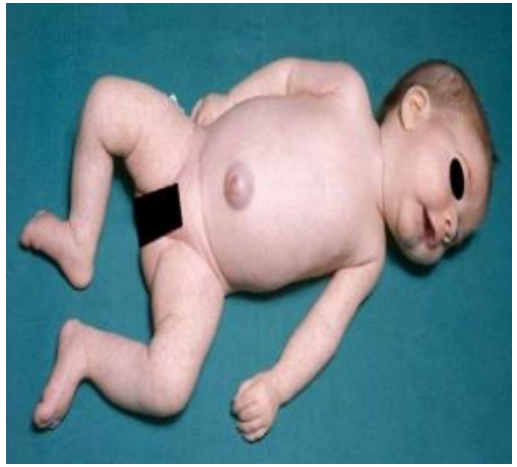
Slip-through on vertical suspension



Draping on horizontal suspension

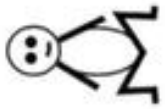
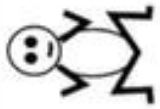
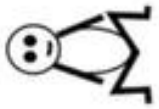
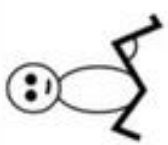


Head lag with arm traction

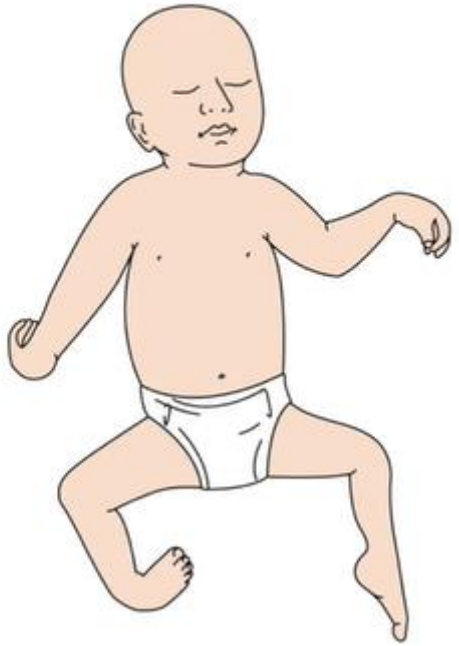


Frog-leg posture

Appendicular Tone

	34 w GA	40 w GA	2 m	5 m	9 m
Scarf sign					
Posture					
Popliteal angle					

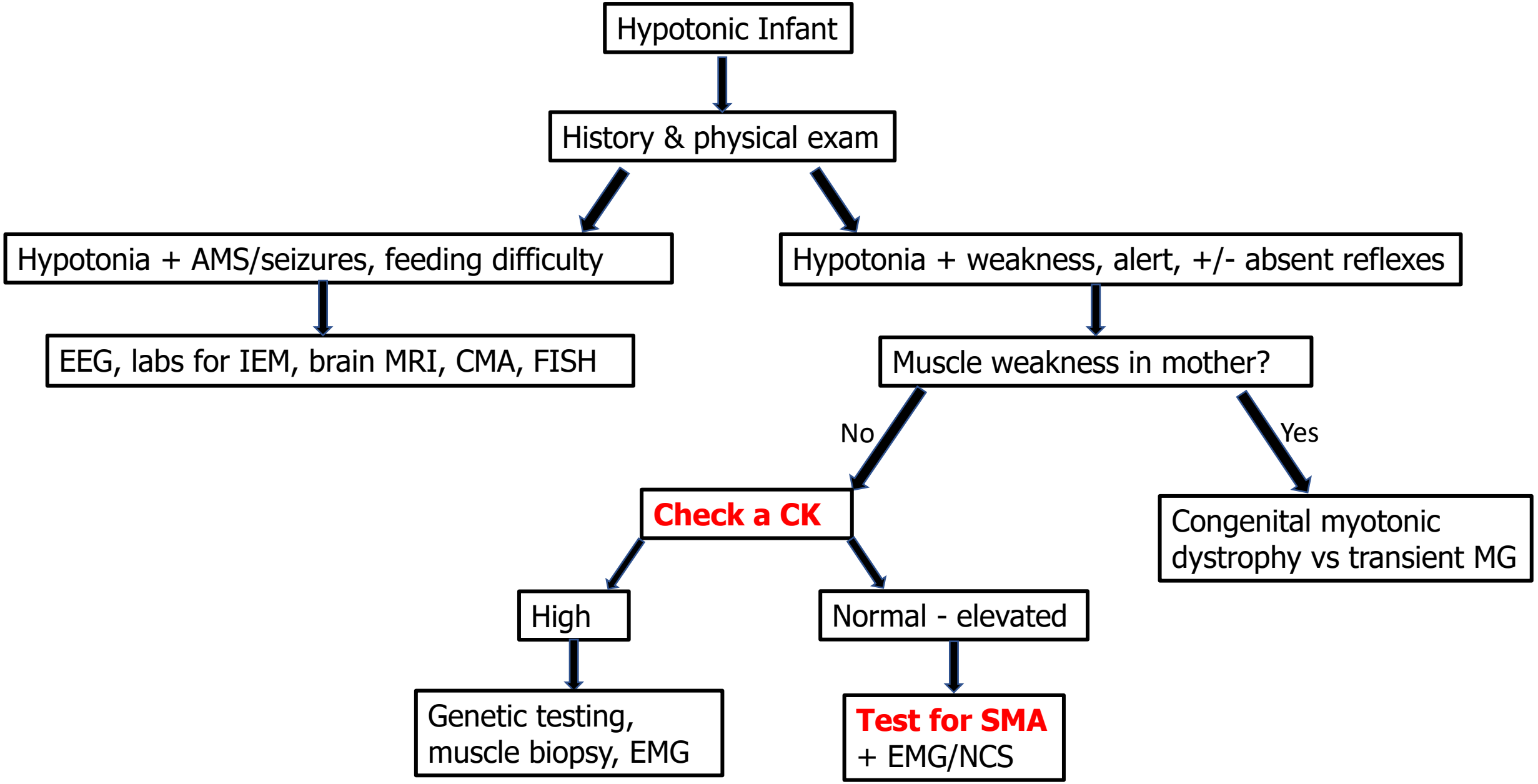
Arthrogryposis



Reflexes

- **Moro reflex/ startle reflex**

- Begins at 28 weeks of gestation
- Initiated by any sudden movement of the neck
- **Elicited by** -- pulling the baby halfway to sitting position from supine & suddenly let the head fall back
- Consists of rapid abduction & extension of arms with the opening of hands, tensing of the back muscles, flexion of the legs and crying



Key: AMS= altered mental status, IEM= inborn error of metabolism, CMA= chromosomal microarray, MG= Myasthenia Gravis, NCS= nerve conduction studies

Part 3: Neuromuscular Disorders presenting in the Neonatal Period

Spinal Muscular Atrophy (SMA)

- Degenerative disorder of motor neurons leading to paralysis and muscle atrophy (without treatment)
- Incidence: ~1/10,000 live births; up to 500 new U.S. cases/year
- Biallelic deletion of *SMN1* gene on chromosome 5q13
- 3 historical clinical subtypes in children – classified by age of onset, developmental milestones achieved, and *SMN2* copy number

SMA Genotype/Phenotype correlate

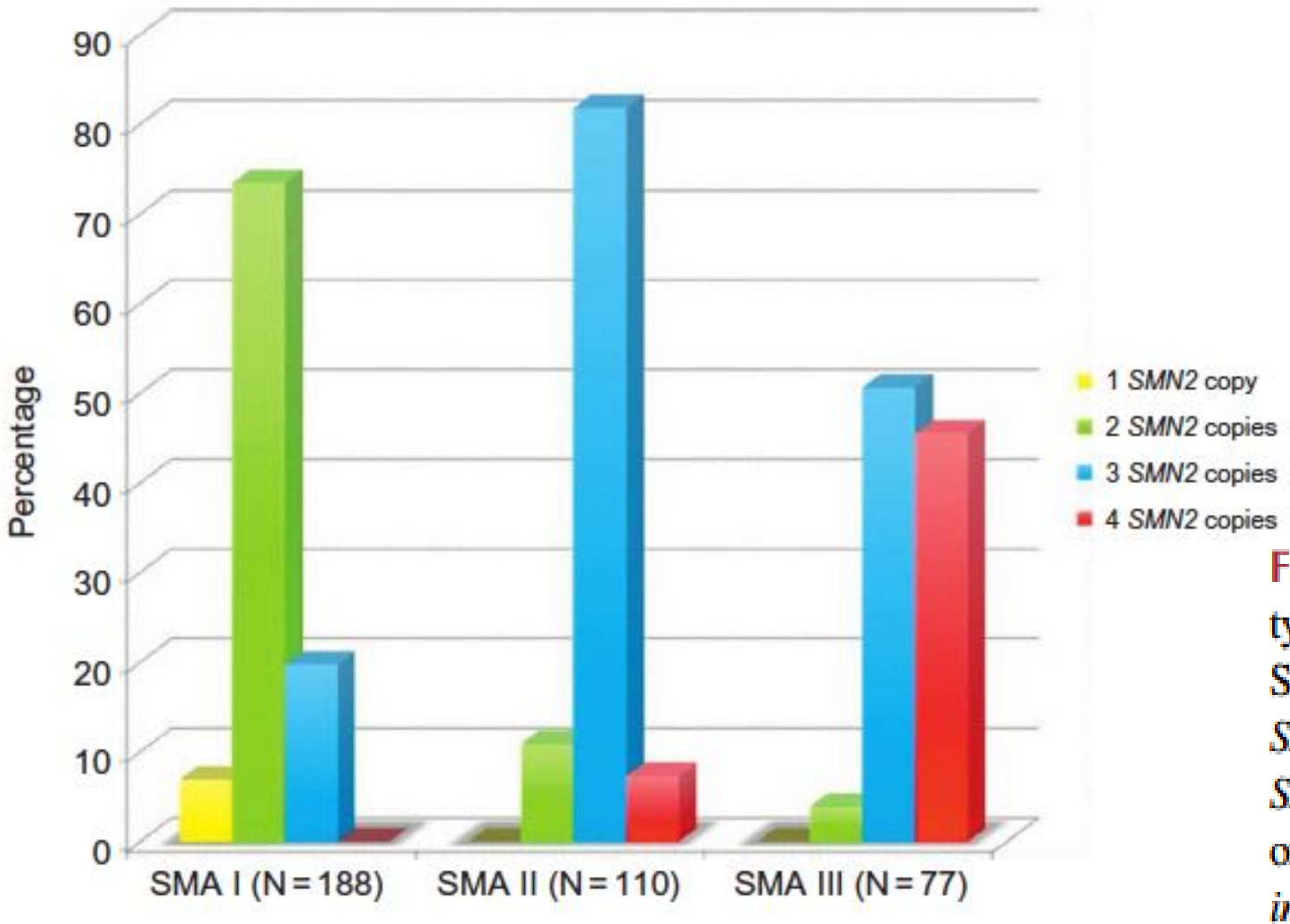
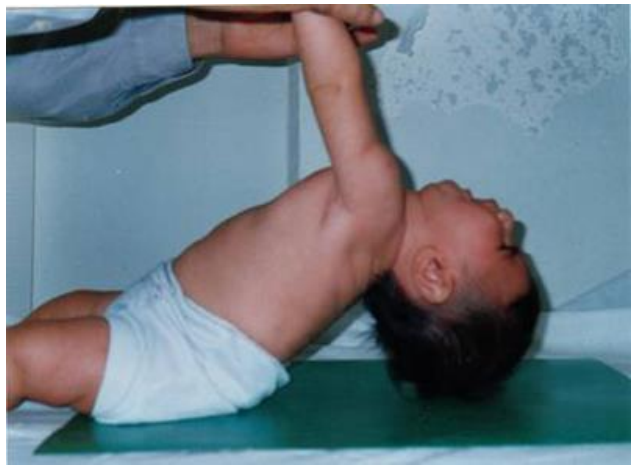


FIGURE 8.2 Frequency of patients with SMA types I, II, and III and *SMN2* copy numbers. In SMA type I, 80% of patients had 1 or 2 copies of *SMN2*, 82% of patients with type II had 3 copies of *SMN2*, and 96% of patients with type III carried 3 or 4 *SMN2* copies. *Modified with permission. This image was published in* American Journal of Human Genetics, *copyright Elsevier (2002).*

SMA Type ‘0’

- Onset in utero and presentation at birth
- Severe weakness, hypotonia, facial weakness, absent reflexes, joint contractures, early respiratory failure (intubated)
- Unlike other types of SMA, may have congenital heart defects
- 0 copies of SMN1, 1 copy of SMN2

Type I SMA
(60% of cases)



- onset <6 months old
- inability to sit
- tongue fasciculations
- areflexia
- suck/swallow difficulty
- early need for vent
- Normal cognition

Type 2 SMA
(27% of cases)

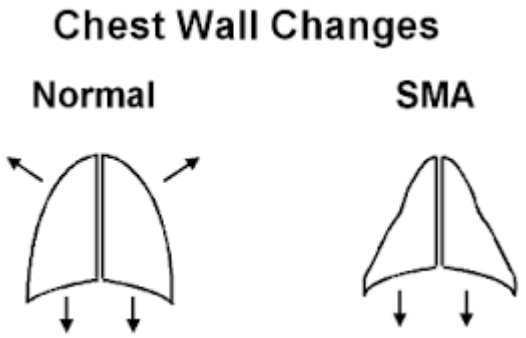
- onset 6-18 months
- inability to stand
- hypotonia
- areflexia
- Progressive scoliosis
- polyminimyoclonus
- Normal cognition

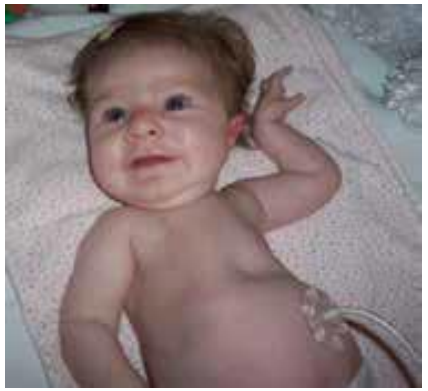
Type 3 SMA
(12% of cases)

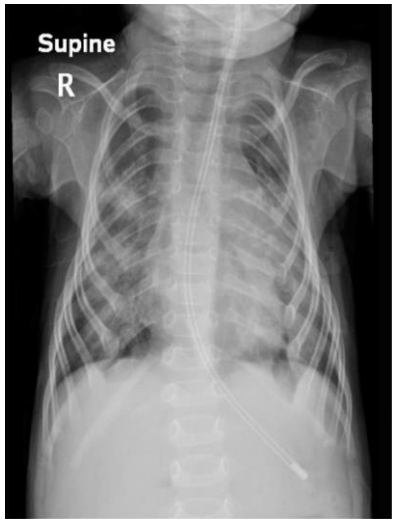
- onset after infancy, often late childhood
- less severe weakness, but can lose ability to walk
- polyminimyoclonus
- Normal cognition

Pulmonary Issues in SMA

- Intercostal muscles weak → ribcage does not expand outward
- Diaphragm pulls the ribcage down "abdominal breathing"
- Infants develop bell-shaped chest with pectus excavatum
- Anatomic changes →lung underdevelopment & weak cough → frequent respiratory infections, nocturnal hypoventilation, and ultimately complete respiratory failure

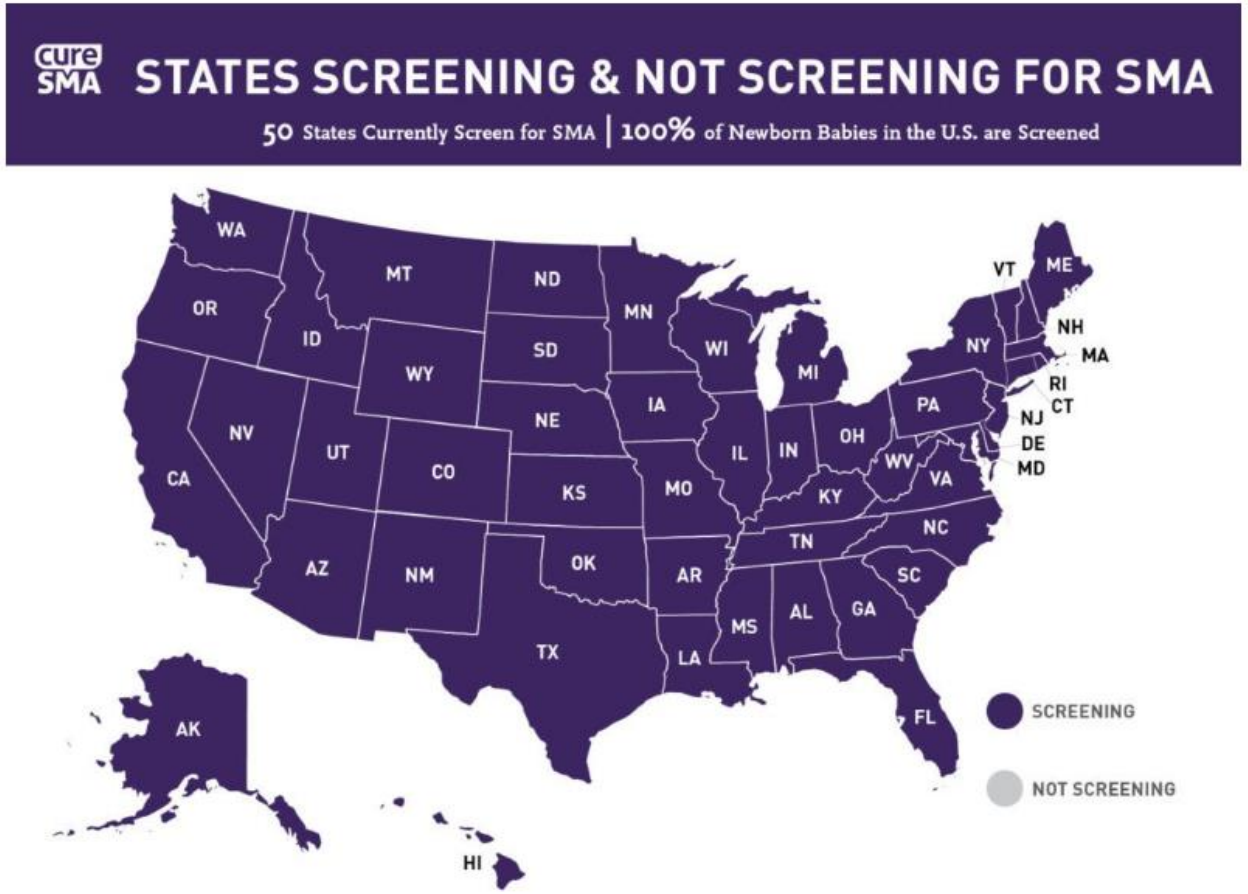






Newborn Screening for SMA

- SMA added to RUSP July 2018
- Added to FL Newborn Screen May 2020



SMA – FDA Approved Therapies

1. Nusinersen
2. Onasemnogene abeparvovec
3. Risdiplam

Nusinersen

- Intrathecal antisense oligonucleotide (ASO)
- 1st FDA approved medicine for treatment of SMA (Dec 2016)
  - Studied in a number of clinical trials in patients with all 3 main clinical types of SMA, as well as pre-symptomatic patients
- Approved for all ages and types of SMA
- $750,000 1st year of use, then $375,000 thereafter
- Requires lifetime therapy

Onasemnogene abeparvovec

- Non-replicating AAV capsid used to deliver a functional copy of the *SMN1* gene intravenously to motor neuron cells
- FDA approved May 2019 following successful clinical trials in symptomatic and pre-symptomatic infants
- Approved for patients with all types of SMA < 2 years of age
- $2.2 million dollars for single dose
- 1 time IV injection; unclear if “wear-off” effect

Risdiplam

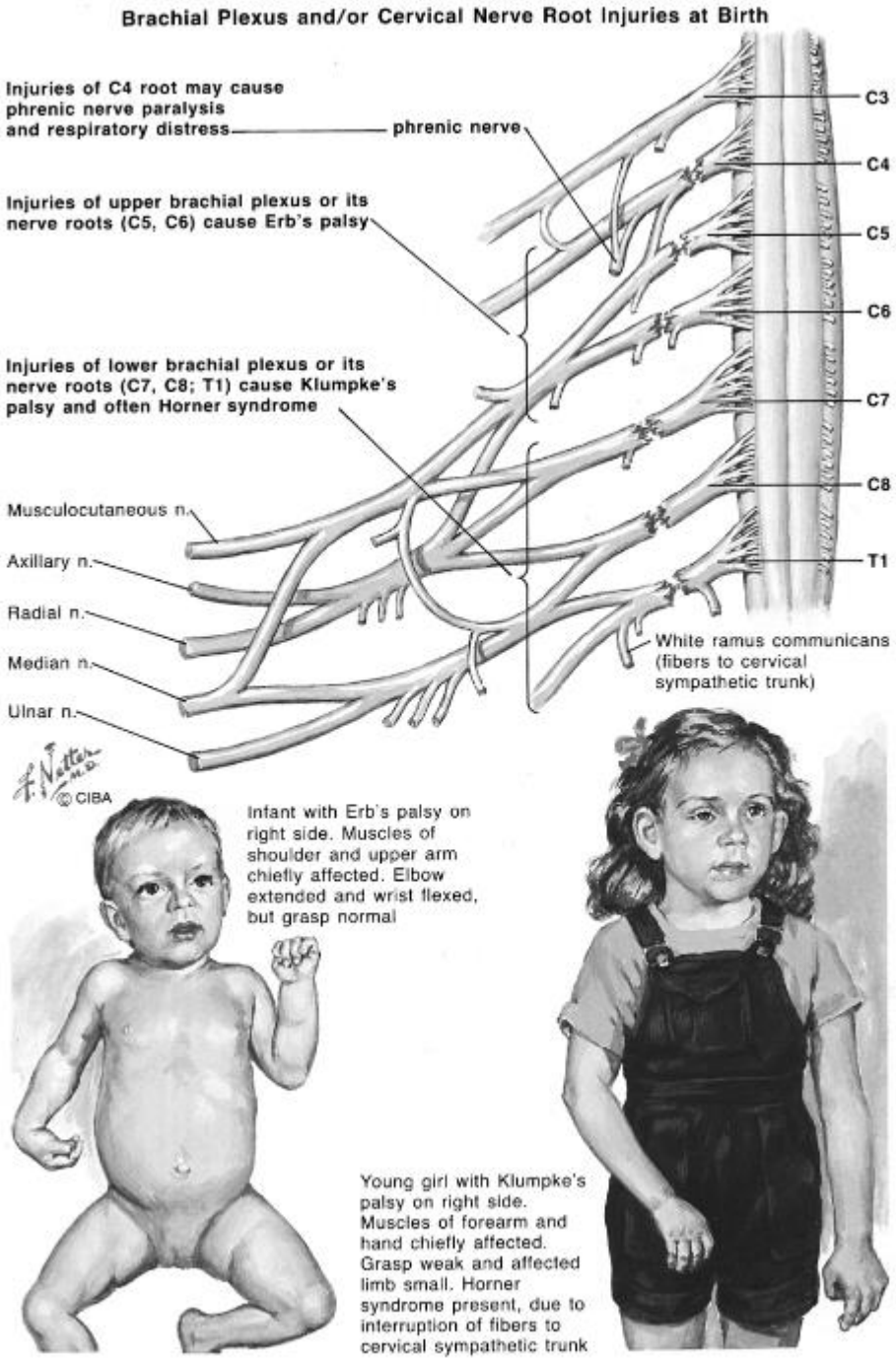
- Orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing to increase SMN protein levels
- FDA approved August 2020 following successful clinical trials in infants and children with SMA
- Approved for patients with all types of SMA and all ages
- Up to $340,000/year (patient weight based)
- Requires lifetime therapy

Congenital Brachial Plexopathy

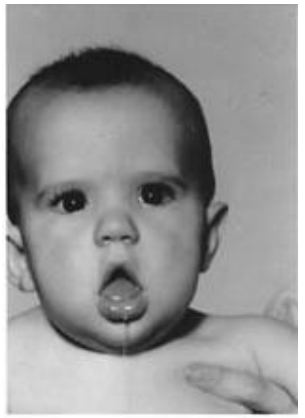
TABLE 12.3 Prognostic Factors for Neonatal Brachial Plexopathy

Poor Prognostic Factors	Good Prognostic Factors	Unknown/Indeterminate Factors
Completely flail upper limb with Horner syndrome (Narakas Group IV)	Recovery of elbow flexion by 2 m	Motor unit recovery: volitional MUAPs in biceps at age 4 m without antigravity elbow flexion
Horner syndrome	Antigravity elbow flexion by age 3m	Clavicular fracture
Phrenic nerve paralysis	No EMG evidence of axonal loss	Narakas Group II (C5, 6, 7)
No recovery of biceps function (elbow flexion) by 3–4 m	Score of >3.5 at 3 m (HSCT scale)	Early recovery of elbow flexion to less than antigravity by age 4 m with subsequent plateau
Score of <3.5 at age 3 m (HSCT scale)	No root avulsion	
Root avulsion	No pseudomeningoceles on MR imaging	
Pseudomeningocele (nerve rootlets absent)		

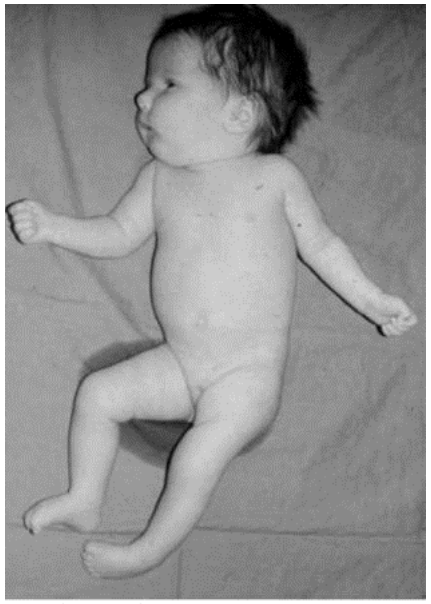
Abbreviations: EMG, electromyography; HSCT, Hospital for Sick Children, Toronto; MRI, magnetic resonance imaging; MUAP, motor unit action potential.



Congenital Myotonic Dystrophy (DM1)



- Neonatal hypotonia, facial weakness, clubfoot, poor feeding
- Prenatal history of polyhydramnios and reduced movements
- Often have respiratory insufficiency and early death
- AD (DMPK gene) – tends to be maternally inherited with more severe phenotype (e.g. intellectual disability) due to anticipation
- Check for weakness and myotonia on mother!

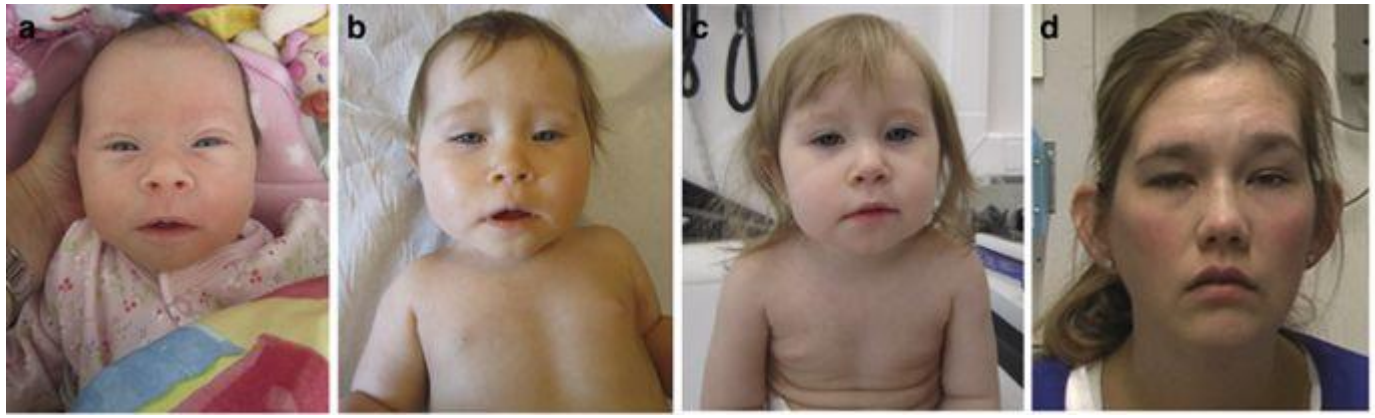


Transient Neonatal Myasthenia Gravis

- 10% of women with MG transmit a transient "neonatal" form of myasthenia gravis to their newborn
- Most neonates weak at birth and recover within a few weeks
- Rare cases of arthrogryposis, respiratory distress and death
- Circulating Abs against the fetal isoform of the AchR
- Maternal Abs disappear with time and fetal isoform of AchR is replaced by the adult isoform during later stages of pregnancy, so outcome is good if baby survives

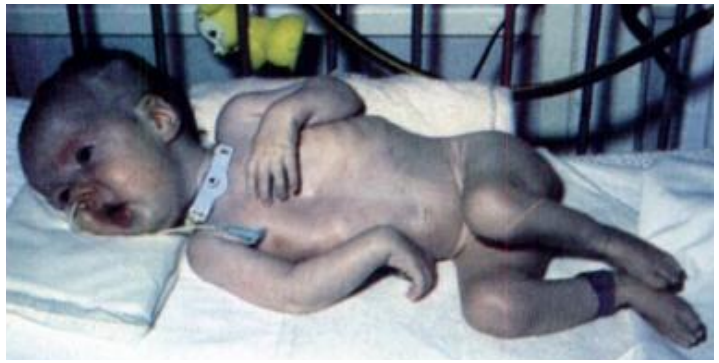
Congenital Myasthenic Syndrome

- History of fatigueable weakness of eye movements, eyelids (ptosis), swallowing, and proximal extremities since infancy
- 19 different genes identified
- Rare with varying degrees of severity
- Some types respond to pyridostigmine, others may be worsened by use of pyridostigmine



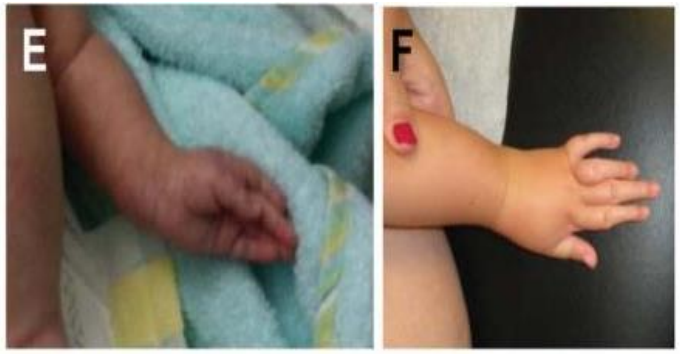
Congenital Myopathy

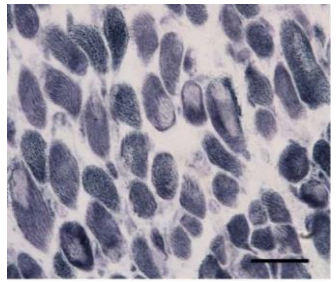
- Rare; prevalence of 1:26,000
- Core myopathy is the most common histopathologic type
- RYR1 is the most common genetic type
- Nemaline myopathy is the most common type presenting in infancy
- Often have normal CK

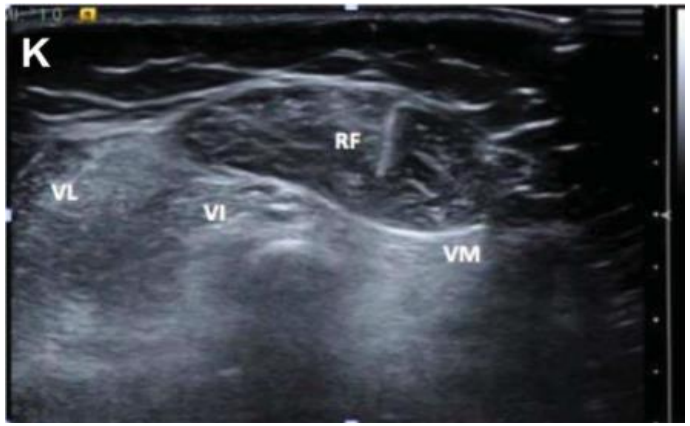


RYR-1 Related Myopathies

- Congenital myopathies: central core (90% of cases), multi-minicore, centronuclear, congenital fiber type disproportion
- Typically presents as congenital hypotonia and proximal LE>UE weakness, with mild facial weakness, joint contracture, EOMI
- Motor abilities improve, followed by prolonged period of stability
- At risk for malignant hyperthermia with exposure to certain anesthetics (succinylcholine, halogenated anesthetics)



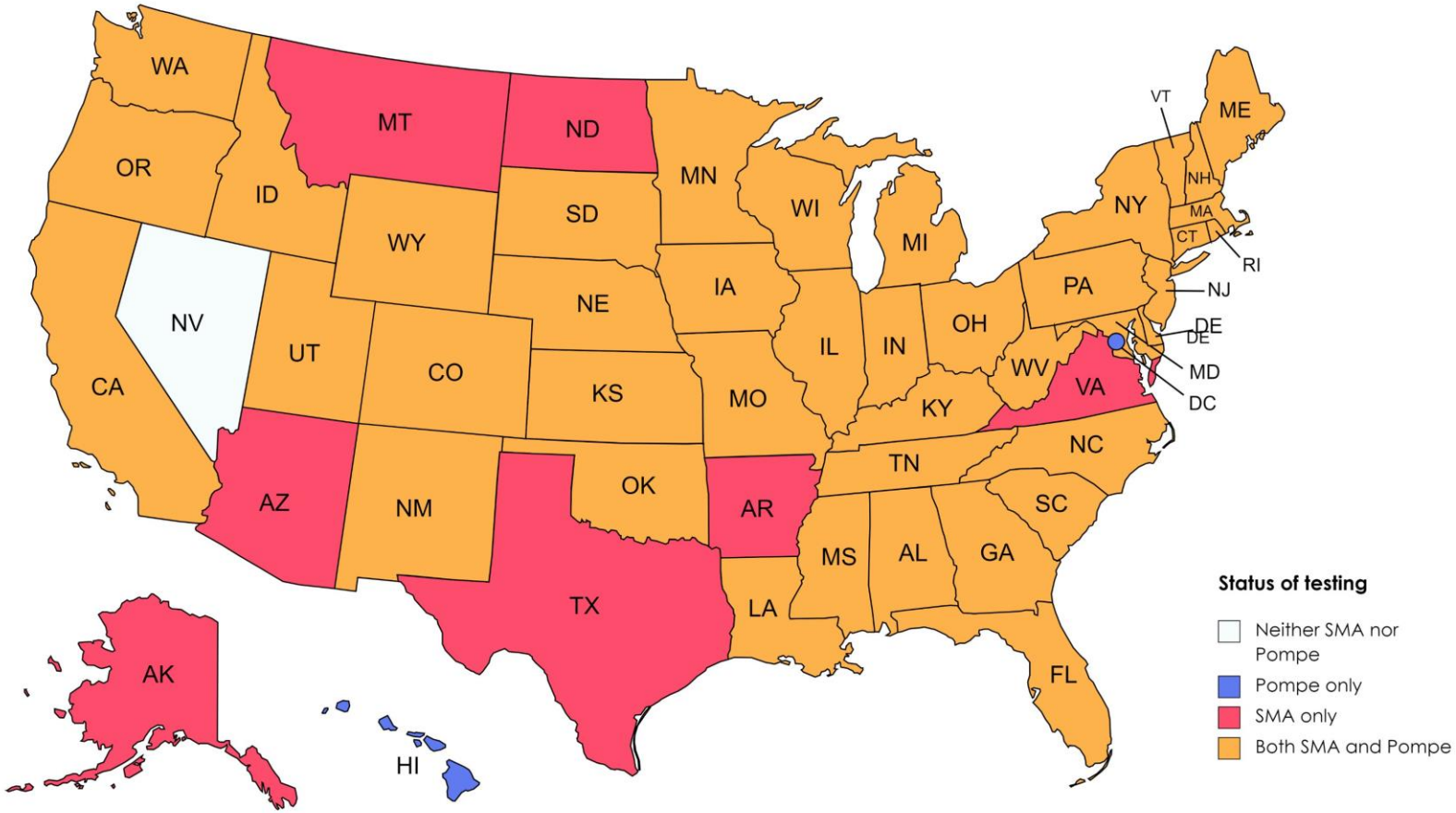




Pompe Disease

- "Metabolic myopathy" due to mutations in GAA gene
- Leads to lysosomal accumulation of glycogen (heart, skeletal muscle)
- Rapidly progressive hypertrophic cardiomyopathy, hypotonia, muscle weakness, respiratory distress, and loss of independent ventilation
- Will see cardiomegaly on chest X-ray, elevated CK
- Treatment: Enzyme replacement helps with heart and lung function >> muscle function
  - critical to start therapy <6 months of age

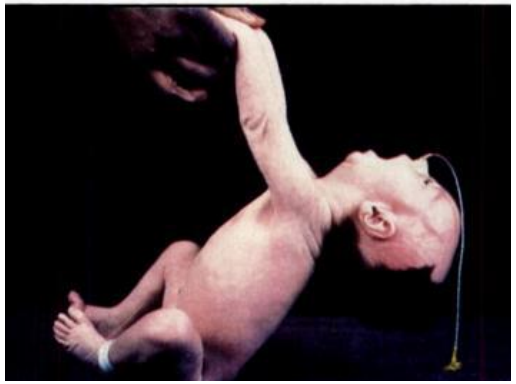
Newborn screen – Pompe Disease

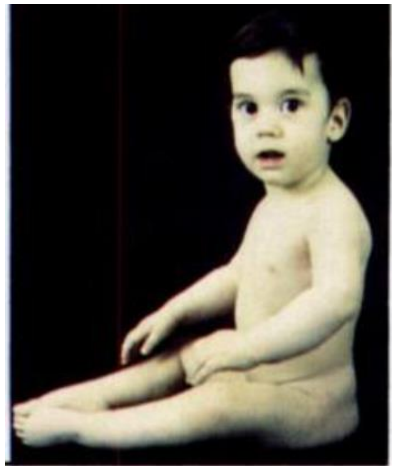


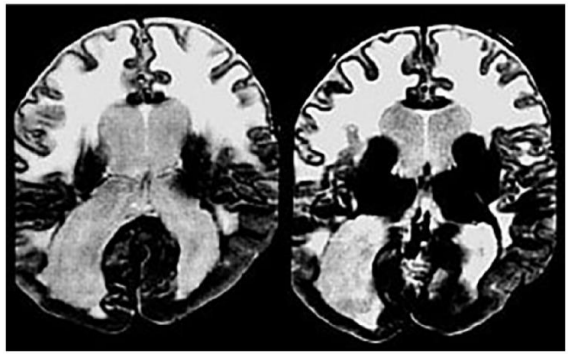
*As of October 2023

Congenital Muscular Dystrophy

- 3 main classifications:
  - Muscle weakness + abnormal brain MRI + cognitive delay
  - Muscle weakness + abnormal brain MRI, no cognitive delay
  - Muscle weakness, normal brain MRI, no cognitive delay
- May have associated skin findings (keratosis pillaris, keloid)
- May gain skills for a period of time, then worsening weakness







Part 4: CASES

Neonatal Neuromuscular Cases

Spinal Muscular Atrophy

Congenital Myotonic dystrophy

Congenital Myasthenic Syndrome

Congenital Myopathy

Transient Myasthenia Gravis

Case 1 – HPI

- Male born at 36 weeks GA via emergent CS due to severe decels
- Uneventful pregnancy; amniotic fluid meconium-stained
- APGARs 2/3/3. Required intubation; Cooled
- Clinical/electrographic seizures during re-warming
- Remains intubated on no sedation

Case 1 – Neuro exam (7 days old)

- MS: awake but not interactive, intubated without sedation
- CNs: EOMI, weak resistance to eyelid opening; ?tongue fasciculations
- Motor: generalized hypotonia, not moving extremities anti-gravity
- Reflexes: absent Moro, absent tendon reflexes

Case 1 – Work-up

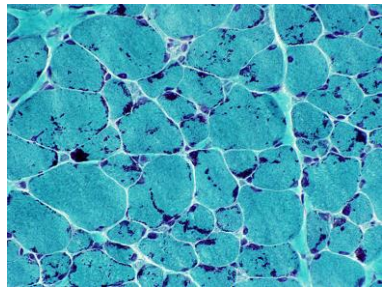
- CK: 298 U/L
- EMG: “The electrophysiologic features are consistent with diffuse motor neuron disease or a sensory/motor axonal neuropathy.”
- Normal brain and total spine MRI

Case 1 – Diagnosis

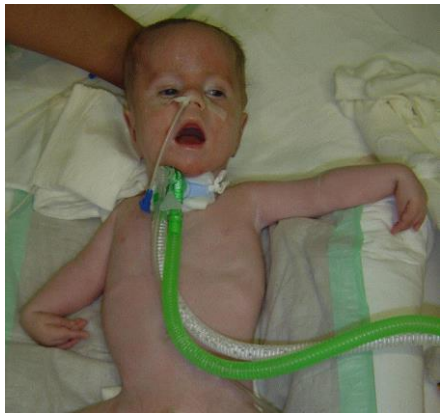
- Genetics:
  - Prader-Willi/Angelman: negative
  - Myotonic dystrophy: negative
  - SMA testing: negative
  - **Congenital myopathy panel:** 2 pathogenic variants in *ACTA1* (c.782A>T, c.217dup)

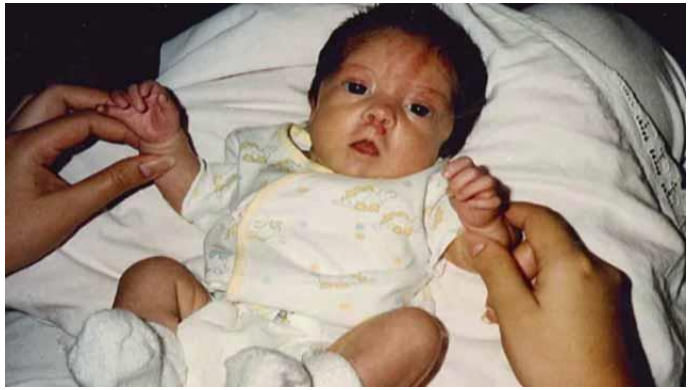
- Diagnosis: **Nemaline myopathy**

Nemaline Myopathy



- Congenital hypotonia, facial weakness, facial dysmorphism (long face, dolicocephaly, high-arched palate), arthrogryposis, club feet
- Poor suck/swallow, severe respiratory involvement at birth
- Incidence 1:50,000; 9 causative genes





Case 2 – HPI

- Male born at 36 weeks GA via SVD with vacuum use
- Pregnancy complicated by severe polyhydramnios (32 weeks)
- APGARs 1/3/5. Required intubation; Cooled for abnormal neurologic exam; Cord pH 7.3, BD -7, lactate 6.1

Case 2 – Neuro exam (5 days old)

- MS: listless, ETT in place
- CNs: pupils constricted, high arched palate
- Motor: moves all extremities weakly, but only distally
- Reflexes: absent throughout
- MSK: left club foot

Case 2 – Work-up

- CK: 254 U/L
- EMG: “The electrophysiological findings are most consistent with a sensory-motor axonal neuropathy. However, because sensory nerve action potentials can be difficult to record in an ICU environment, SMA or other motor neuron disease should also be considered
- Brain MRI: subgaleal hematoma

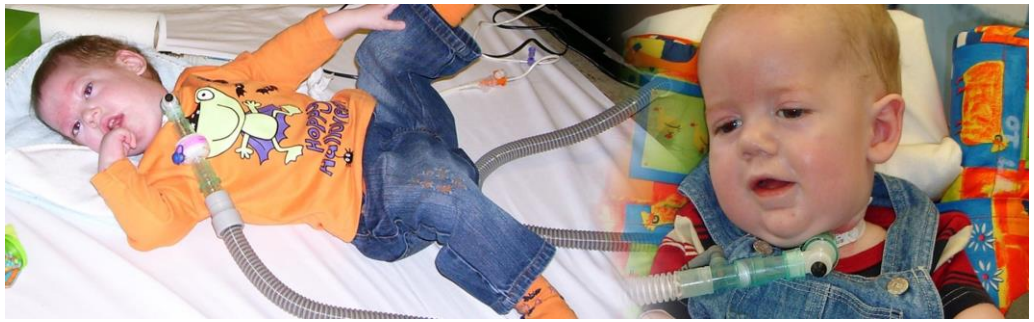
Case 2 – Diagnosis

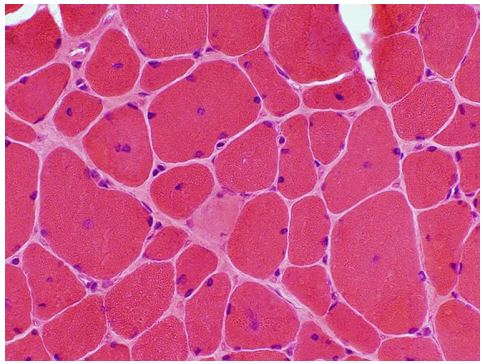
- Genetics:
  - Chromosomal microarray: normal
  - SMA testing: normal
  - Myotonic dystrophy testing: negative
  - Neuromuscular disorders panel: pathogenic variant in *MTM1* (c.503delA)

- Diagnosis: **X-linked myotubular myopathy**

X-linked Myotubular Myopathy

- Congenital hypotonia, facial weakness, poor suck/swallow, severe respiratory involvement at birth
- Rare





Case 3 – HPI

- Male born at 38 weeks GA via repeat CS
- Pregnancy unremarkable; no reported decreased movements
- Delivery notable for meconium stained fluid. APGARs 7/8. Grunting and cyanosis requiring 7L FiO2 100%, transferred
- Noted at birth to have dysmorphic features including retrognathia, arachnodactyly, finger contractures, rocker bottom feet; also with murmur

Case 3 – Neuro exam (5 days old)

- MS: alert, awake, looks around
- CNs: EOMI, face slightly weak, high arched palate
- Motor: axial hypotonia with head lag; ulnar deviation at the wrists, finger contractures, feet in eversion; anti-gravity strength at elbows, wrists, hips, knees, and ankles
- Reflexes: 2+ throughout (normal)
- MSK: retrognathia, arachnodactyly, rocker bottom feet

Case 3 – Work-up

- CK: 152 U/L
- EMG: “This is a limited EMG/NCS in a 2-month-old male with electrophysiological evidence most suggestive of a myopathy”
- Brain MRI: normal

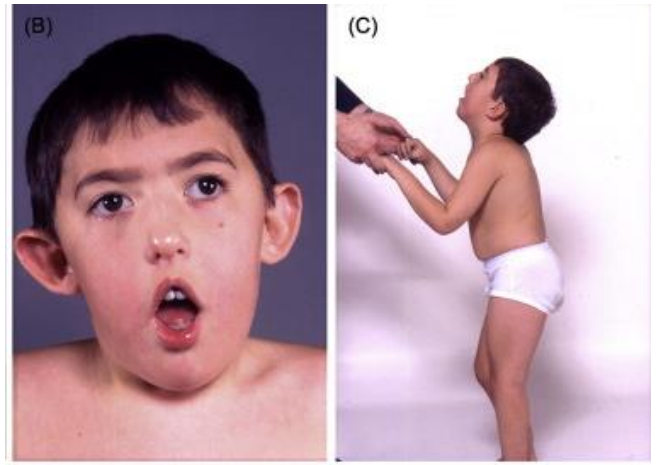
Case 3 – Diagnosis

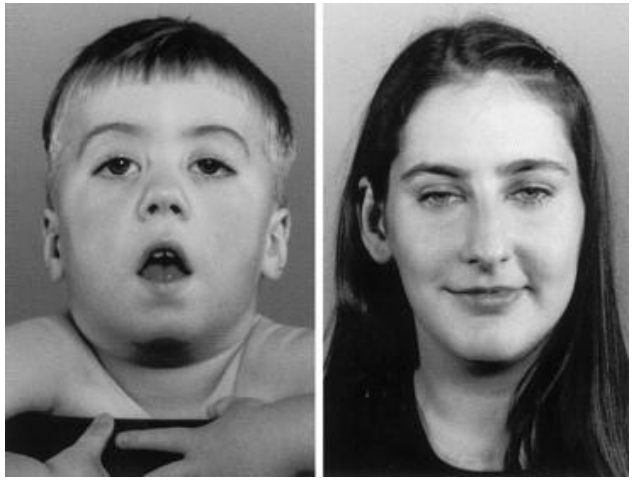
- Genetics:
  - Chromosomal microarray: negative
  - Neuromuscular disorders panel: VUS in COL6A
  - Posthumous WES: 2 pathogenic variants in *RAPSN*

- Diagnosis: **Congenital myasthenic syndrome**

RAPSYN Congenital Myasthenic Syndrome

- In most patients, symptoms are present at birth or infancy
- 1/3 of patients have arthrogryposis or other congenital malformations
- Respiratory infections or other febrile illness precipitate increased weakness and respiratory crises and can cause an anoxic encephalopathy
- Can treat with pyridostigmine





Case 4 – HPI

- Male born at 39 weeks GA via CS for breech
- Pregnancy notable for reduced fetal movements
- APGARs 1, 4. Low tone and inadequate respiratory effort requiring intubation in the DR
- No dysmorphic features noted

Case 4 – Neuro exam (0 days old)

- MS: alert, awake, looks around
- CNs: PERRL, EOMI, minimal facial movements, +tongue fasciculations
- Motor: axial and appendicular hypotonia; muscle atrophy of all extremities; minimal movements of arms, no movements of legs
- Reflexes: absent
- MSK: arm flexion contractures

Case 4 – Work-up

- Newborn screen: 0 copies SMN1
- Chromosomal microarray: normal
- EMG: “Abnormal limited study. There is electrophysiologic evidence of severe, subacute to possibly chronic active denervation in the upper and lower extremities, most suggestive of a diffuse motor neuron disease.”

Case 4 – Diagnosis

- Diagnosis: **Spinal Muscular Atrophy, type 0**

Case 5 – HPI

- Female born at 31 weeks GA via C-section for breech
- Pregnancy complicated by maternal drug use (THC, meth, cocaine)
- Perinatal complications: placental abruption
- Delivery notable for chest compressions x1 minute, intubated
- APGARs 2/5/7. Not eligible for cooling protocol due to GA

Case 5 – Initial exam (1 day old)

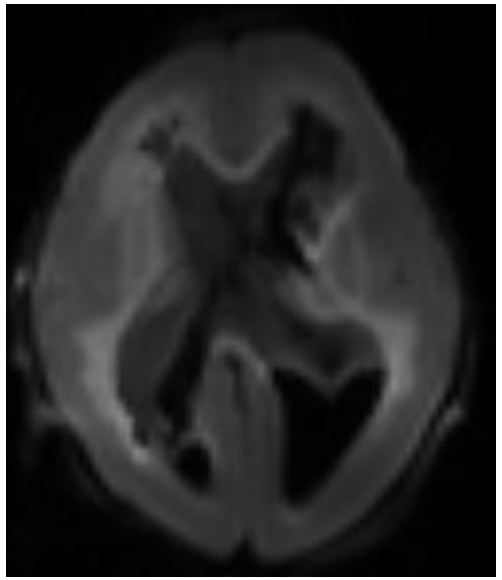
- Mental status: intubated but not sedated
- CNs: pupils equal, EOMI, no nystagmus
- Motor: moderate-severe hypotonia, decreased movement, seems to move LLE>RLE
- Reflexes: no suck elicited, absent grasp, absent deep tendon reflexes

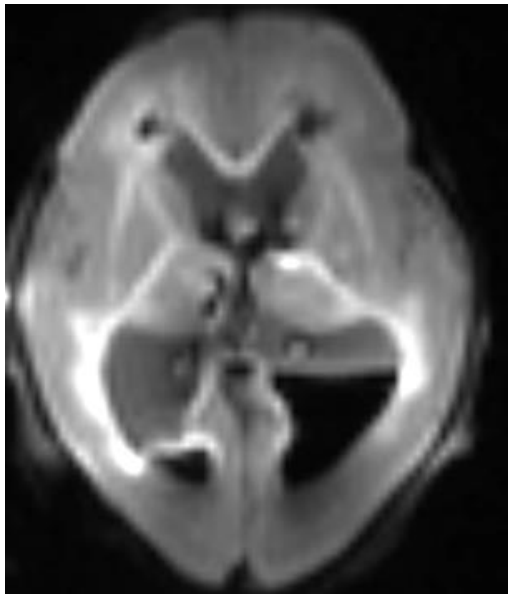
Case 5 – Initial work-up

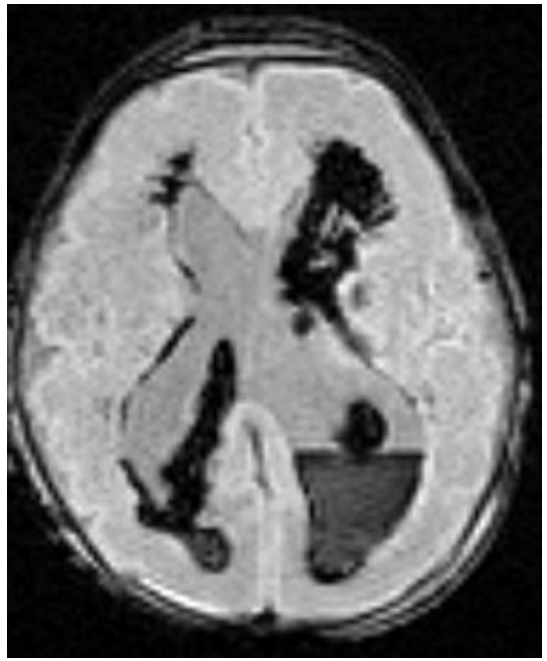
- Genetic testing (CMA, SMA, PWS, neuromuscular disorders): pending

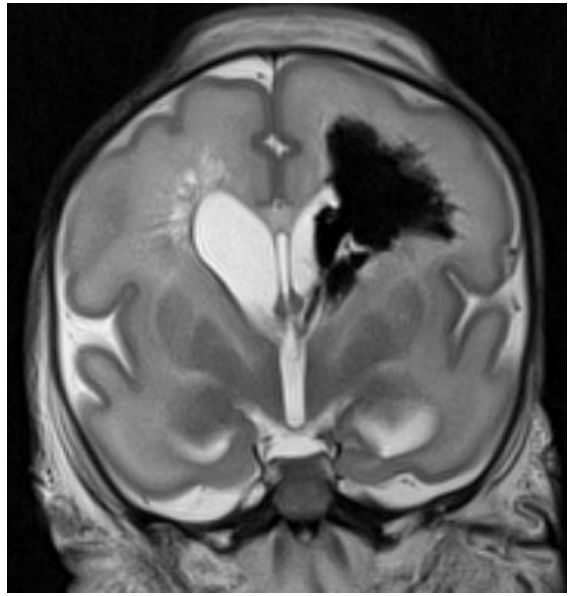
Case 5 – Neuro exam (6 days old)

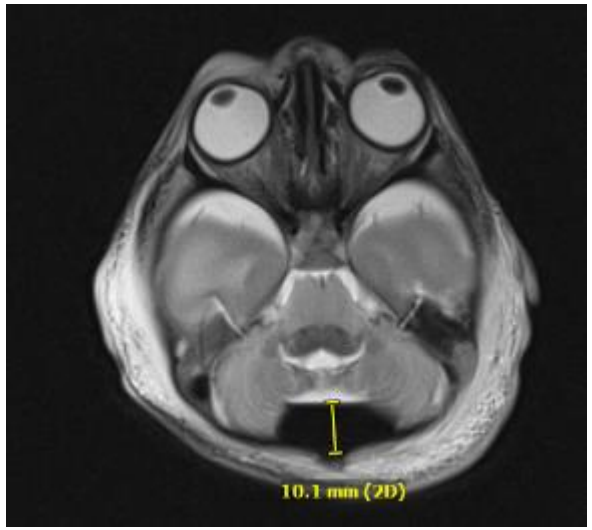
- MS: unresponsive to painful stimuli (intubated without sedation)
- CNs: pupils 3mm and sluggishly reactive, dolls eyes intact, no clearly visible tongue fasciculations
- Motor: generalized hypotonia, does not move limbs spontaneously, withdraws right foot slightly and inconsistently from tactile stimulation; no other withdrawal responses in other extremities
- Reflexes: absent tendon reflexes
- Sensory: does not withdraw from touch or painful stimuli

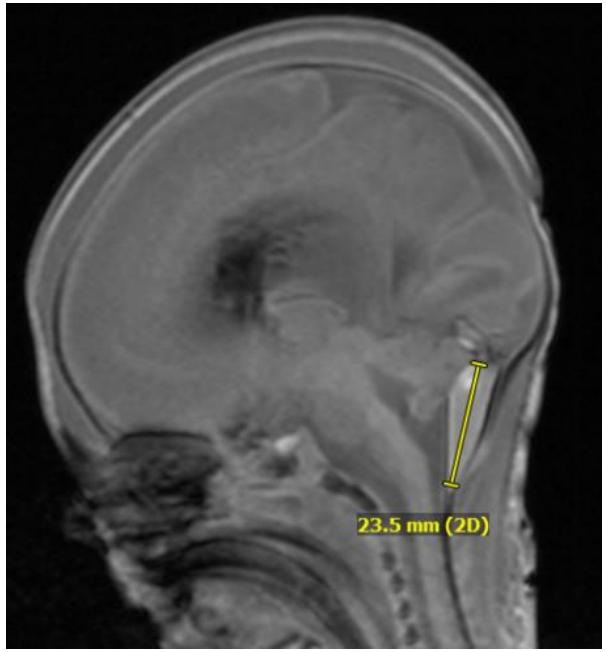









10.1 mm (2D)


23.5 mm (2D)

Case 5 – Further Work-up

Brain MRI

- severe ventriculomegaly
- bilateral intraventricular hemorrhages, left greater than right, with intraparenchymal extension bilaterally greatest at the left centrum semiovale.
- increased periventricular T2 hyperintense signal most consistent with the previously reported periventricular leukomalacia.
- diffusion restriction involving the periventricular region likely related to the intraparenchymal hemorrhage.
- In addition there is layering of blood products within the posterior fossa posterior to the cerebellum and extending down to the level of the foramen of magnum. This is causing local mass effect upon the medial and posterior aspect of the cerebellum. This hematoma is up to 10 mm in thickness and extends 2.4 cm in craniocaudal dimension. No other areas of hemorrhage are seen.

TAKE HOME POINTS

1. Hypotonia can exist without weakness. Presence of weakness suggests (but is not diagnostic of) a neuromuscular disorder
2. Central hypotonia is typically axial (head lag, slip-through); peripheral hypotonia is typically axial and appendicular (decreased resistance to passive movement of extremities)
3. A normal CK does not rule out a neuromuscular disorder
4. Treatment exists for SMA and congenital myasthenic syndrome, so early diagnosis is key