Neonatal Hypotonia

Basil T. Darras, M.D.
Neuromuscular Center
Boston Children's Hospital
Harvard Medical School
Boston, MA, USA

Financial Disclosures

- Dr. Darras is the author of articles regarding neuromuscular diseases for UpToDate, Inc. UpToDate does not produce health-care related products or services.
- Dr. Darras has served on SABs for Sarepta, Inc., AveXis, Inc., Biogen, Inc., Cytokinetics, Inc., Roche, Inc., and Vertex, Inc.
- Research support from the National Institutes of Health/National Institute of Neurological Disorders and Stroke, the Slaney Family Fund for SMA, Working on Walking Fund, and the SMA Foundation; grants from CureSMA, Ionis Pharmaceuticals and Biogen during ENDEAR, CHERISH, CS1/CS2, CS10/CS12 and CS11 studies, AveXis, Cytokinetics, Fibrogen, PTC, Roche, Santhera, Sarepta, and Summit; BTD reports no personal financial interests in these companies.

Hypotonia and neuromuscular disorders

Outline

- Hypotonia
  - Definition
  - Assessment
- Neuromuscular diseases in the hypotonic infant and child
- Hypotonia
  - Stepwise diagnostic approach

Muscle tone

Definition

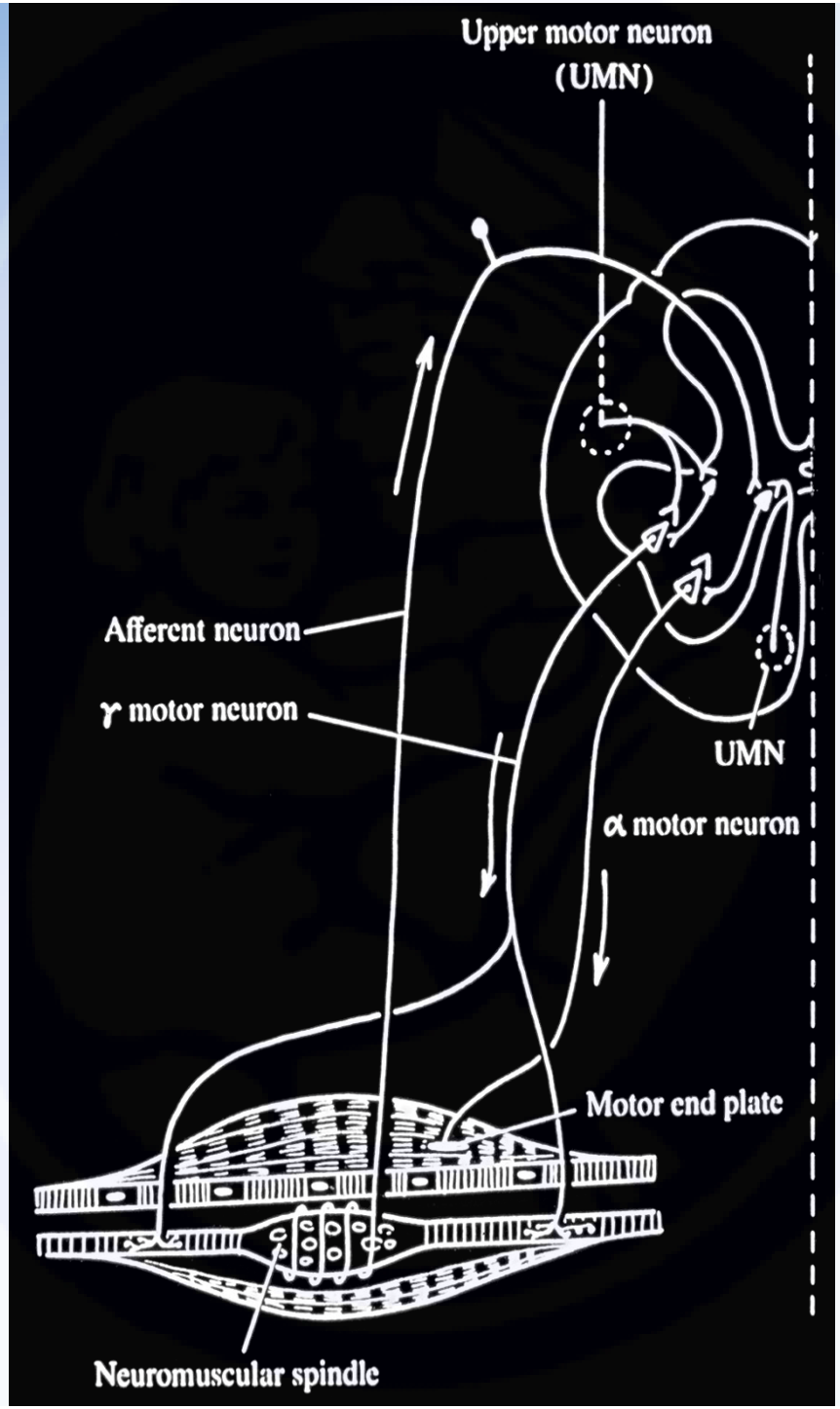
Muscle tone is the resistance of muscle to stretch

- Postural tone (i.e. antigravity)
- Phasic tone

Hypotonia

Definition

Reduction in postural tone (i.e. antigravity), with or without an alteration in phasic tone (tendon reflexes)



Hypotonia

Differential anatomic diagnosis

- Brain
- Spinal cord
- Anterior horn cell
- Peripheral nerve
- Neuromuscular junction
- Muscle fiber

Hypotonia

Assessment

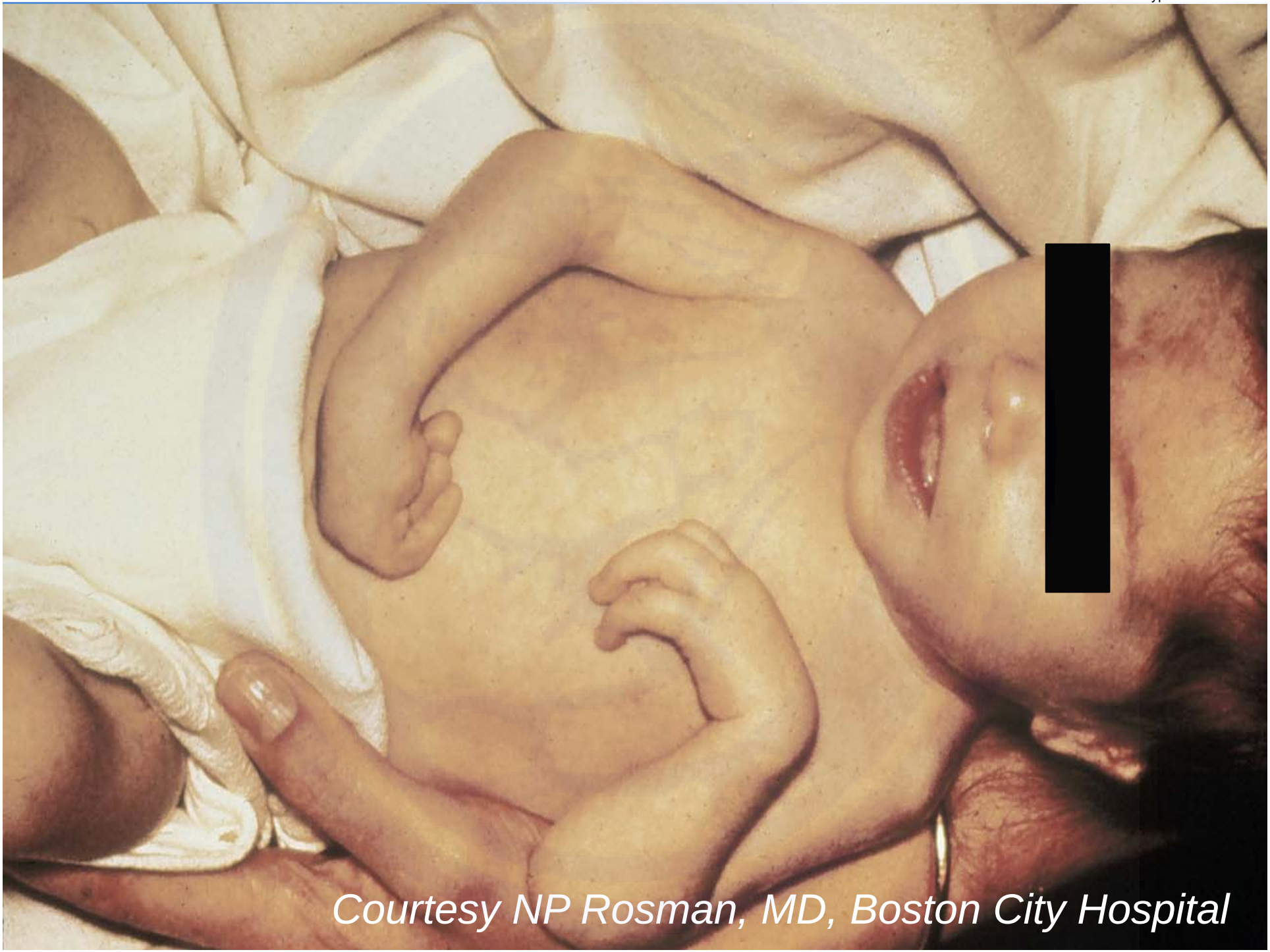
- History
- Physical examination
  - General physical examination
  - Motor examination
  - Primary neonatal reflexes
  - Sensation
  - Hypotonia-focused examination

General physical examination

- Normal examination
- Dysmorphic features
- Organomegaly
- Cardiac failure
- Abnormalities of genitalia
- Respiratory irregularities/failure
- Dislocation of the hips
- Arthrogryposis

Hypotonia *in utero*

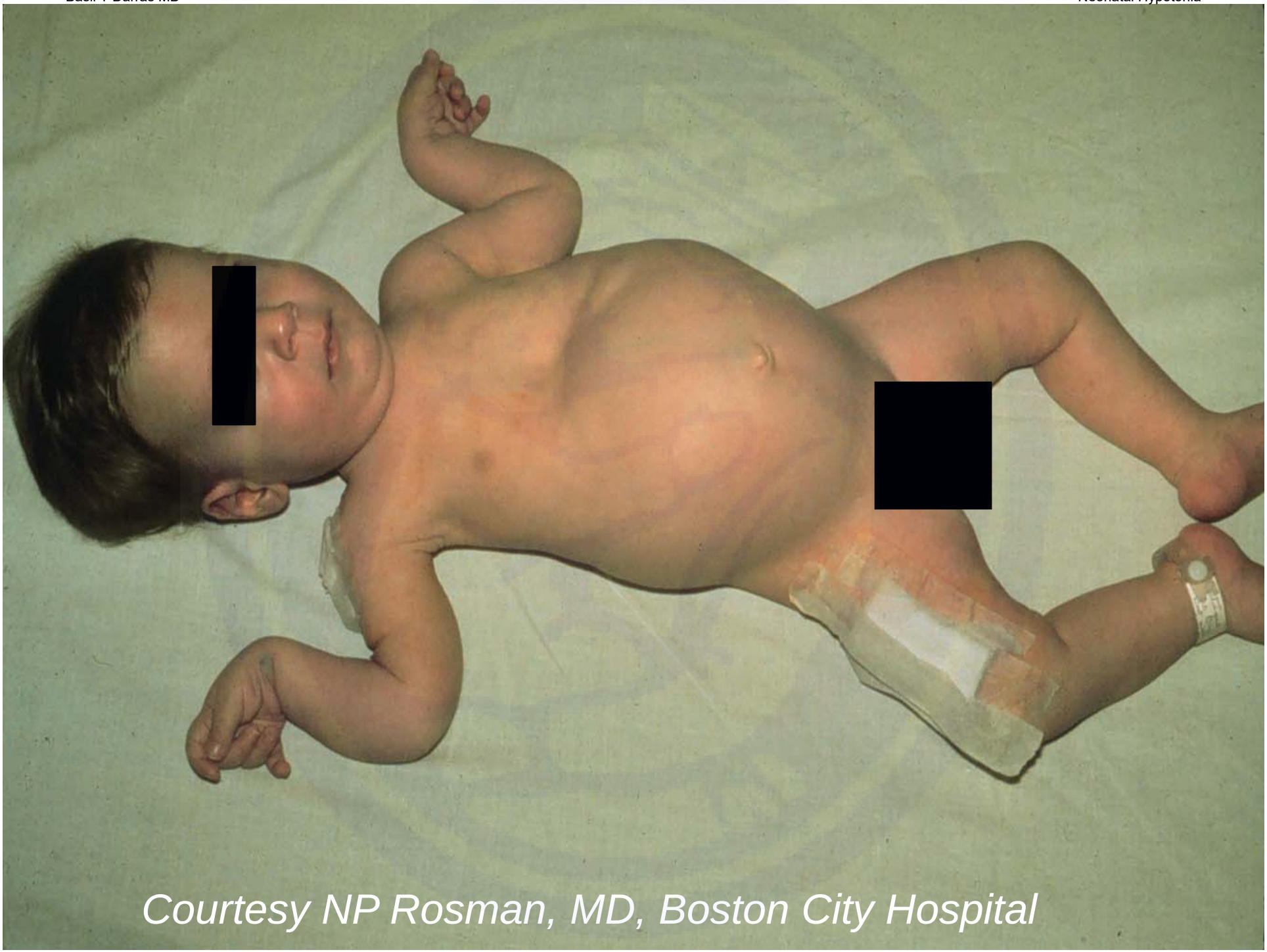
- Dislocation of the hips
- Arthrogryposis



Hypotonia

Physical examination

- General physical examination
- Passive manipulation of the limbs
- Muscle power, muscle stretch reflexes
- Appearance (flaccid), motility (e.g.antigravity)
- Neonatal reflexes, sensation
- Traction response ("head lag")
- Vertical suspension ("slips through")
- Horizontal suspension ("drapes over")
- "Scarf" sign, "Heel to ear or chin"



Courtesy NP Rosman, MD, Boston City Hospital

Hypotonia

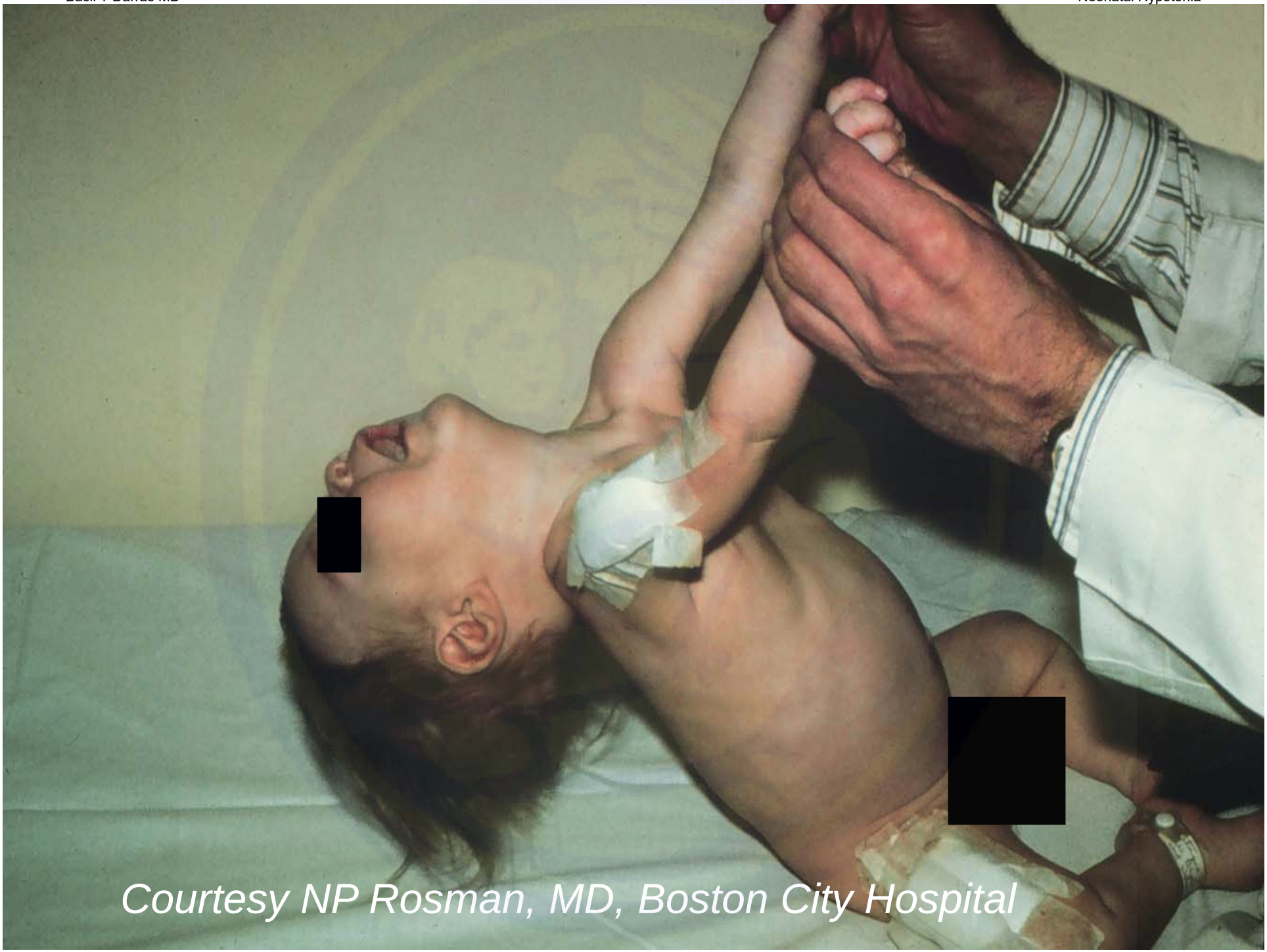
Physical examination

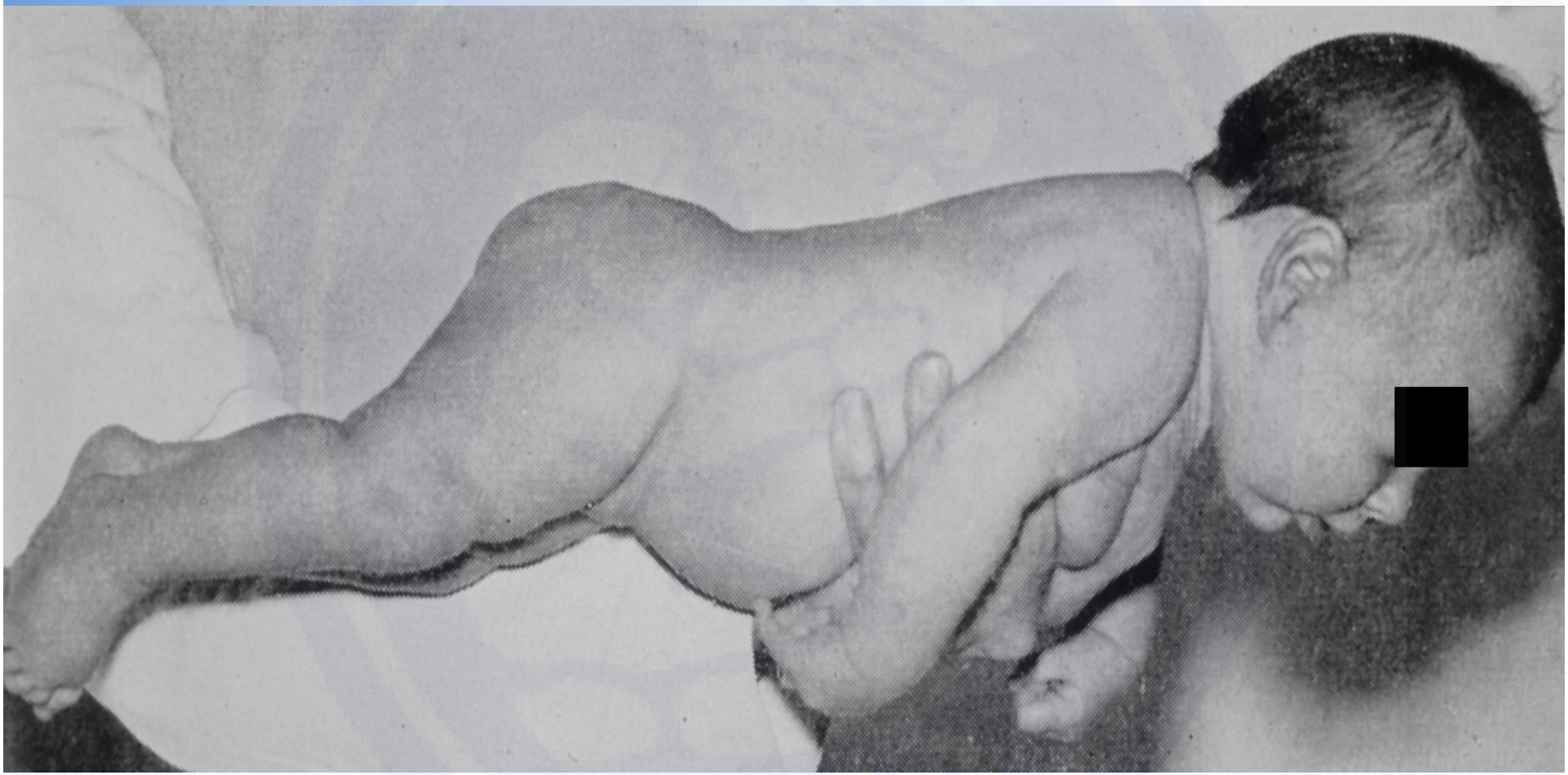
- General physical examination
- Passive manipulation of the limbs
- Muscle power, muscle stretch reflexes
- Appearance (flaccid), motility (e.g.antigravity)
- Neonatal reflexes, sensation
- Traction response (“head lag”)
- Vertical suspension (“slips through”)
- Horizontal suspension (“drapes over”)
- “Scarf” sign, “Heel to ear or chin”

Hypotonia

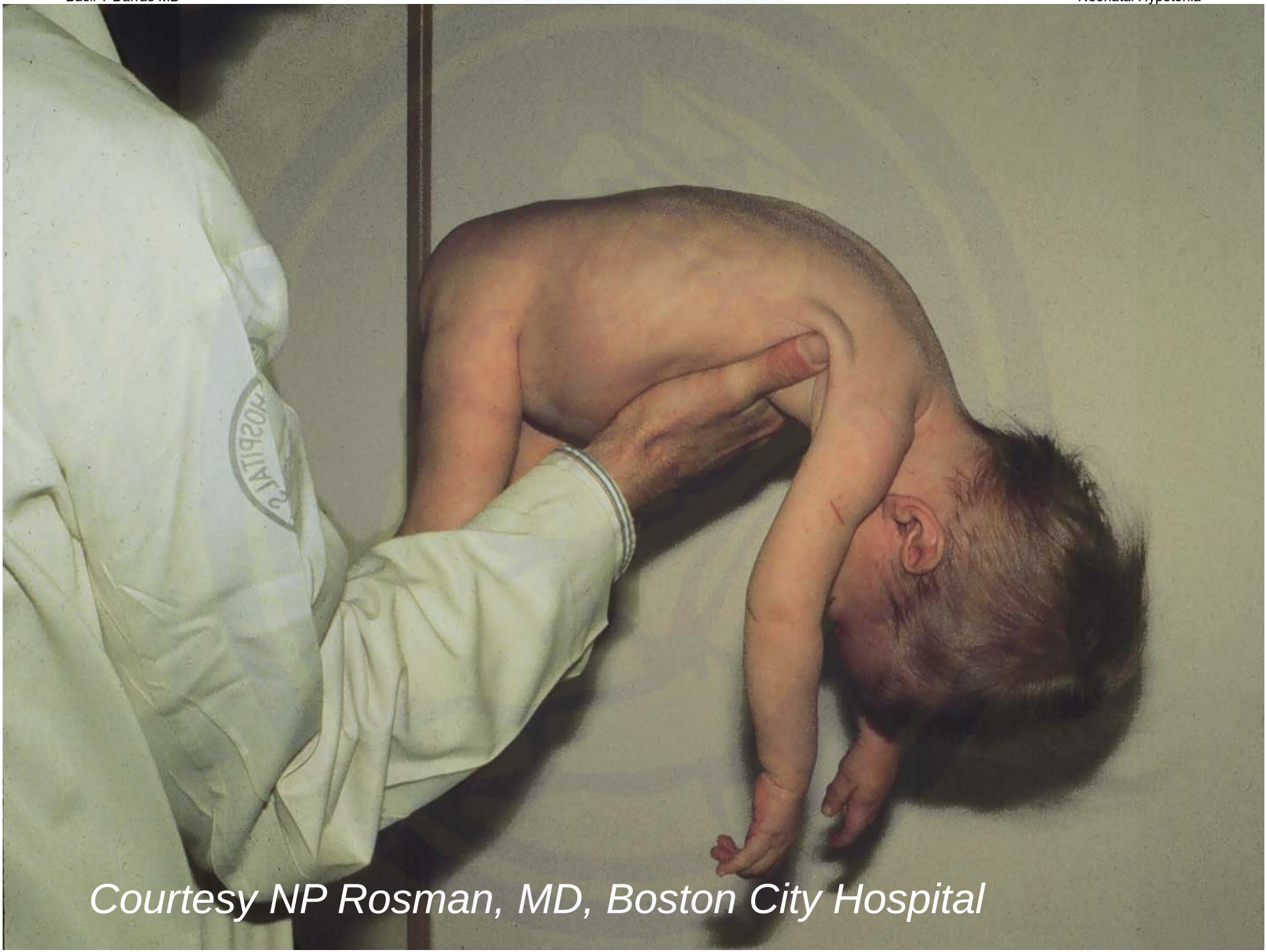
Physical examination

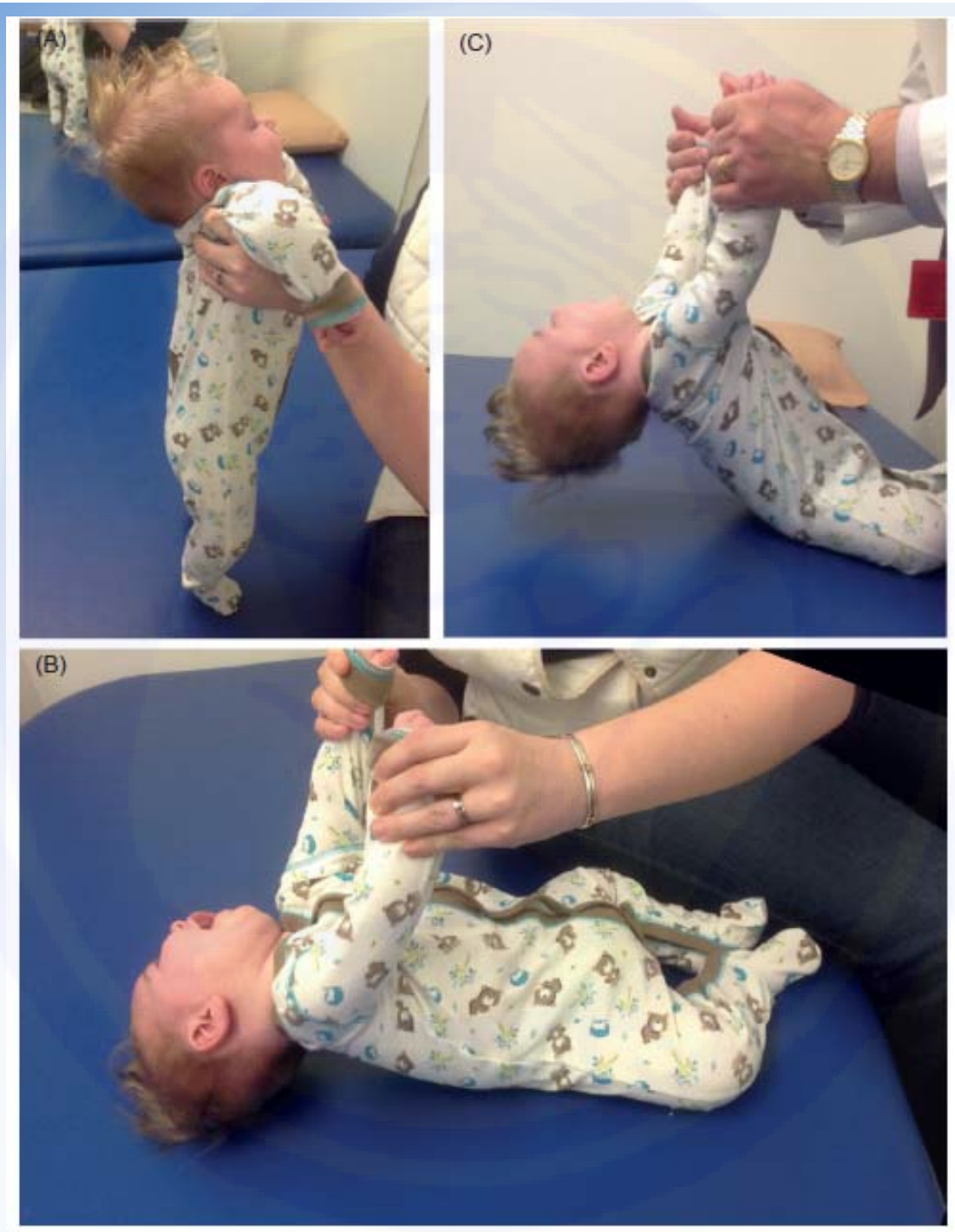
- General physical examination
- Passive manipulation of the limbs
- Muscle power, muscle stretch reflexes
- Appearance (flaccid), motility (e.g.antigravity)
- Neonatal reflexes, sensation
- Traction response (“head lag”)
- Vertical suspension (“slips through”)
- Horizontal suspension (“drapes over”)
- “Scarf” sign, “Heel to ear or chin”

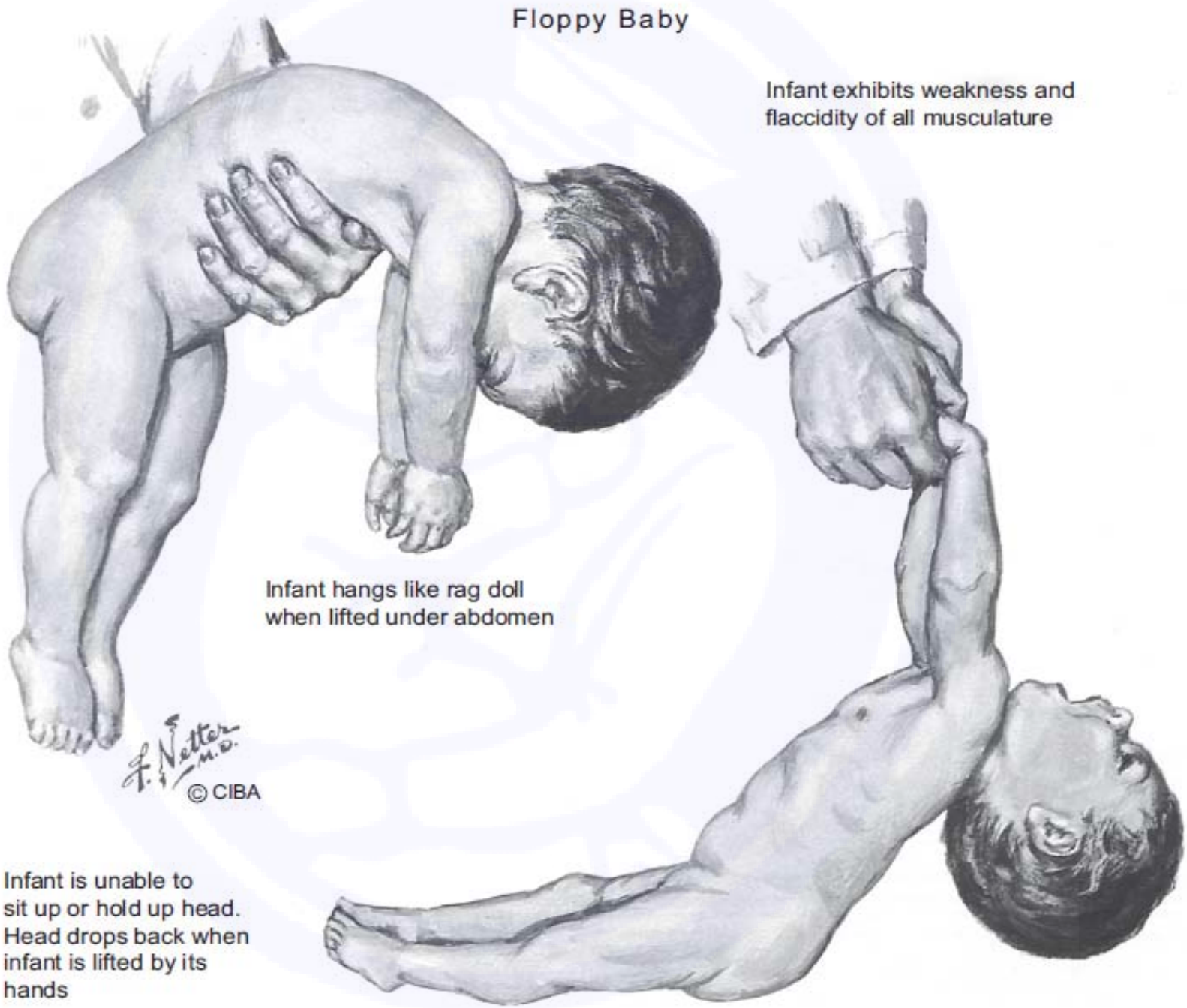




Courtesy NP Rosman, MD, Boston City Hospital







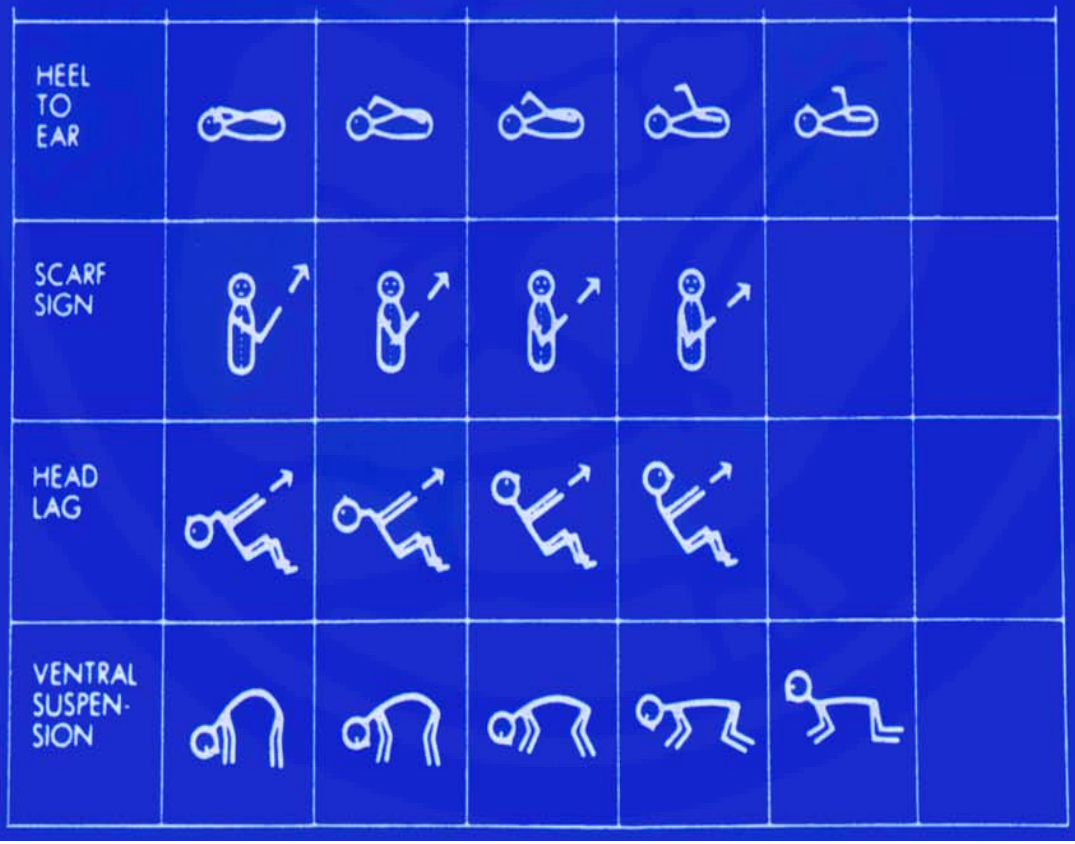
Hypotonia

Physical examination

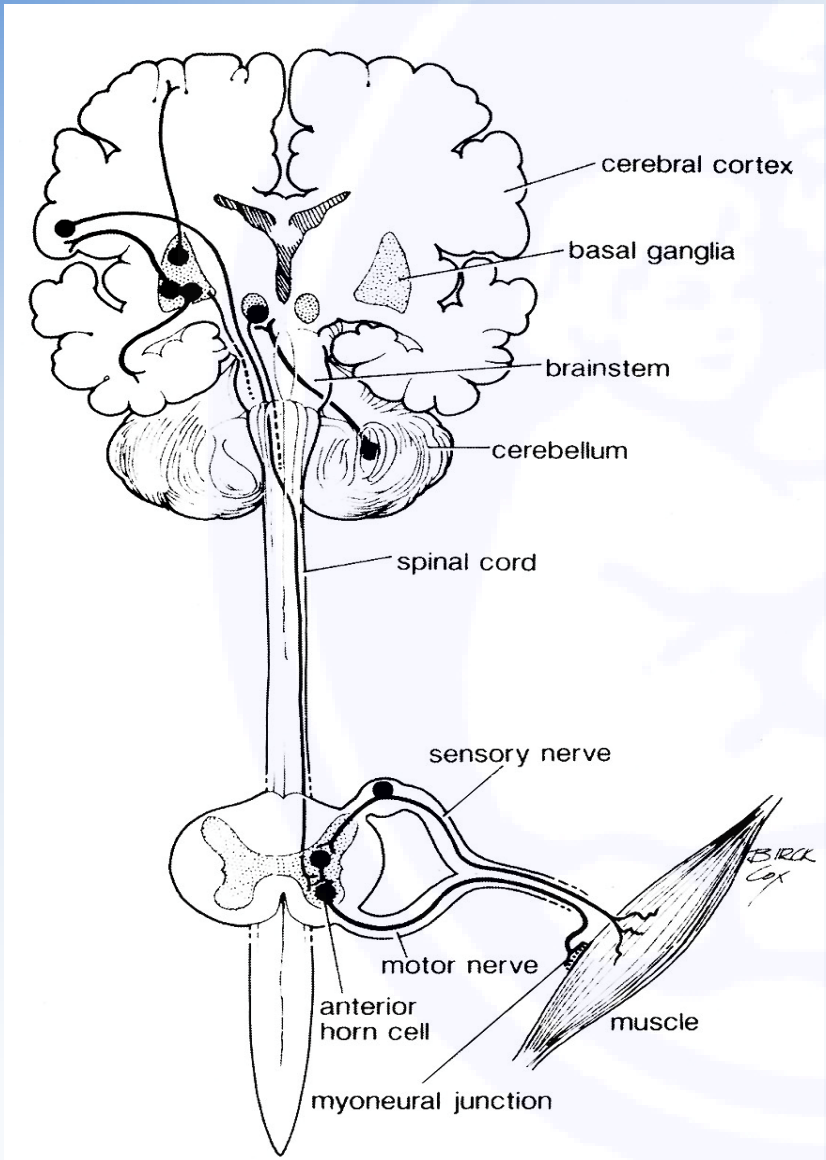
- General physical examination
- Passive manipulation of the limbs
- Muscle power, muscle stretch reflexes
- Appearance (flaccid), motility (e.g.antigravity)
- Neonatal reflexes, sensation
- Traction response (“head lag”)
- Vertical suspension (“slips through”)
- Horizontal suspension (“drapes over”)
- “Scarf” sign, “Heel to ear or chin”

HYPOTONIA

PHYSICAL EXAMINATION



Approach to diagnosis



- Cerebral or central hypotonia

  (about 2/3)

- Lower motor unit or peripheral hypotonia

  (about 1/3)

Cerebral (central) hypotonia

- History consistent with a CNS insult
- Global developmental delay, seizures
- Microcephaly, dysmorphic features
- Malformation of other organs

❑ *Weakness less than degree of hypotonia (non-paralytic hypotonia)*

❑ *Movement through postural reflexes*

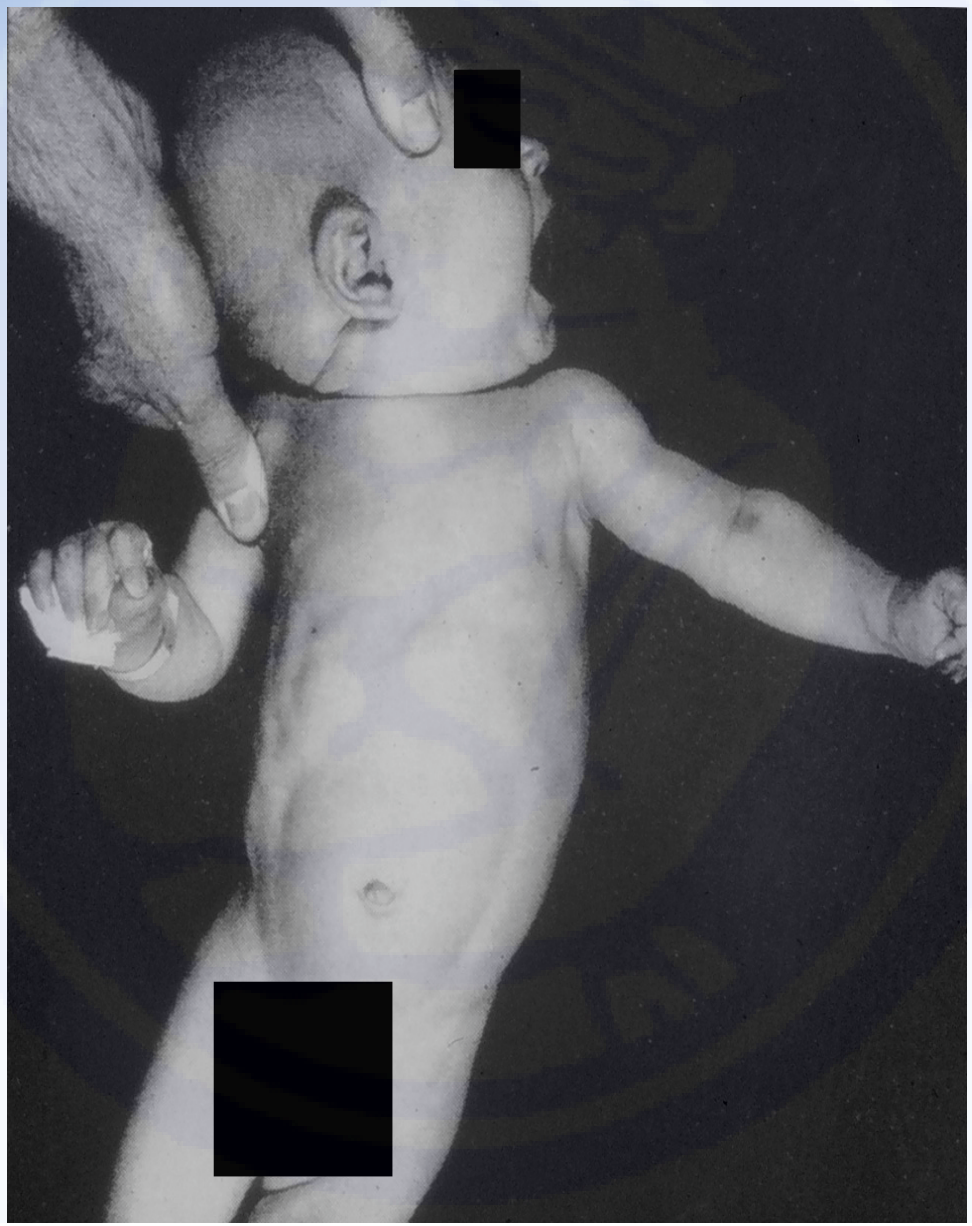
❑ *SRs: Normal or brisk, clonus, Babinski sign*

❑ *Brisk and/or persistent infantile reflexes*

ATNR

FIG. 7
The asymmetrical tonic neck reflex.

ATNR



Lower motor unit (peripheral) hypotonia

- No abnormalities of other organs
- No global delay, delayed gross motor development
- Muscle atrophy, fasciculations

❑ *Weakness in proportion/excess to hypotonia (paralytic hypotonia)*

❑ *Decreased antigravity limb movements*

❑ *Failure of movement on postural reflexes*

❑ *Absent or depressed SRs*

Combined cerebral and motor unit hypotonia

- Congenital myotonic dystrophy
- Congenital muscular dystrophies
- Peroxisomal disorders
- Leukodystrophies
- Mitochondrial encephalomyopathies
- Neuroaxonal dystrophy
- Familial dysautonomia
- Asphyxia secondary to motor unit disease

Hypotonia

Systemic diseases

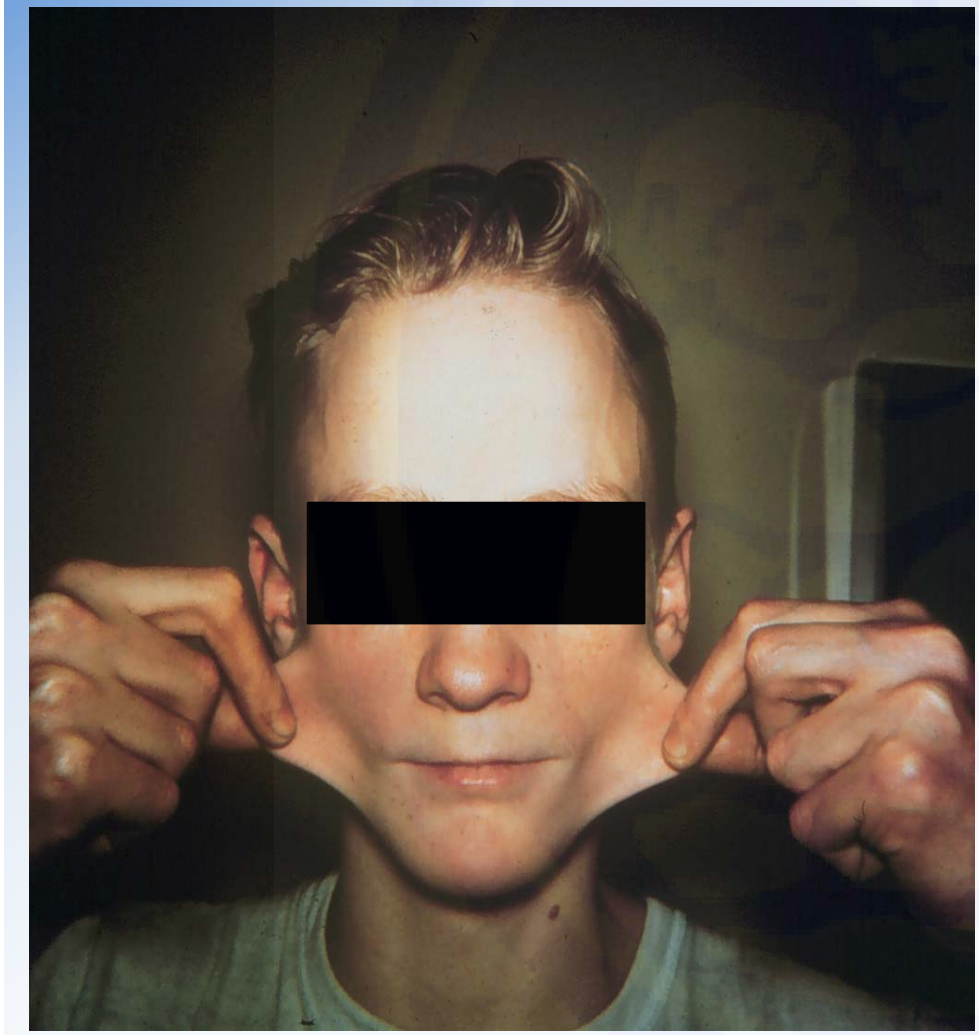
- Sepsis
- Congenital heart disease
- Hypothyroidism
- Rickets
- Malabsorption, malnutrition
- Renal tubular acidosis

Muscle tone

Determinants

- Gamma/alpha motor system
- Visco-elastic properties of muscle
- Joint and tendon resistance

Hypotonia



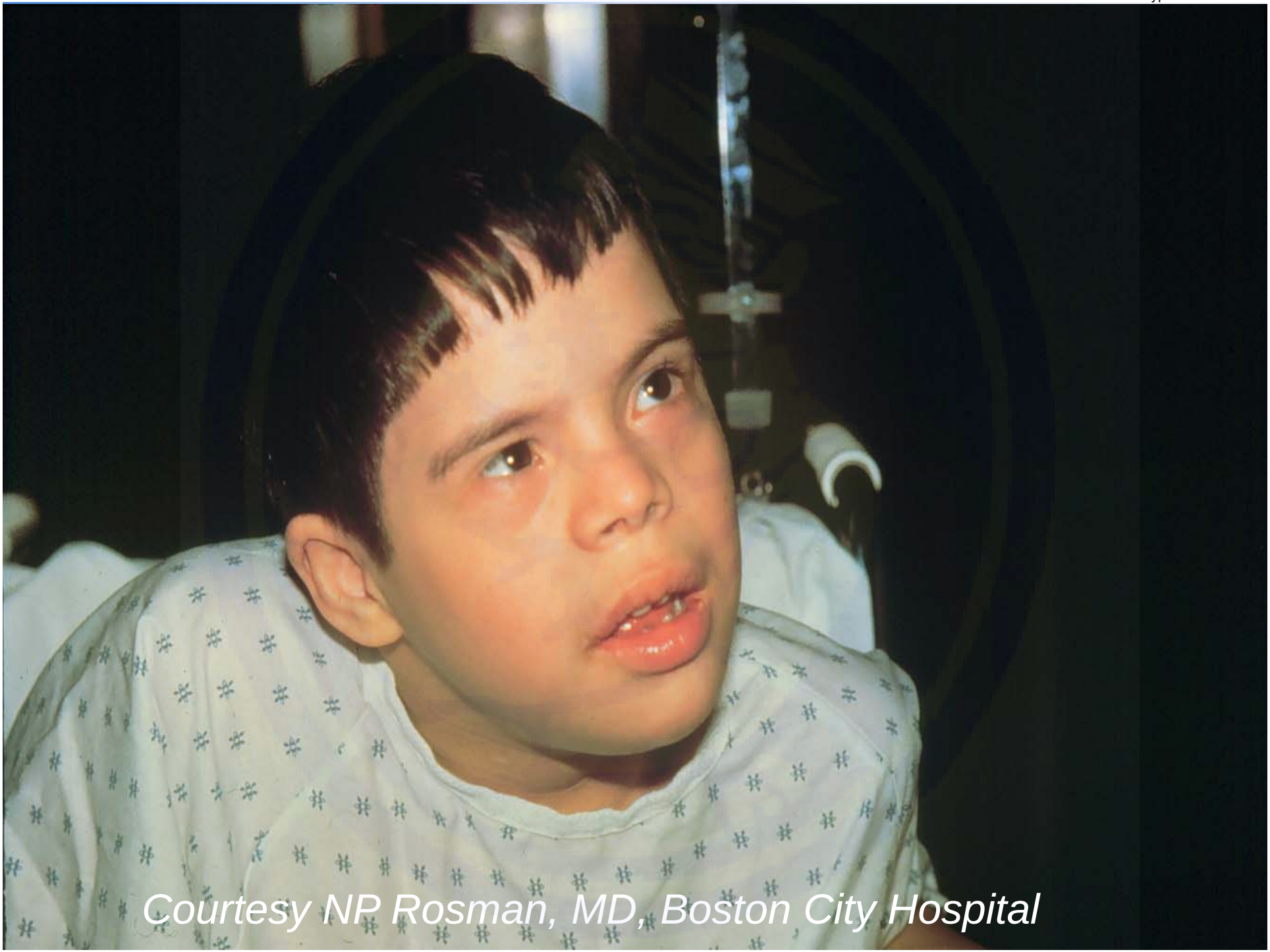
Connective tissue disorders

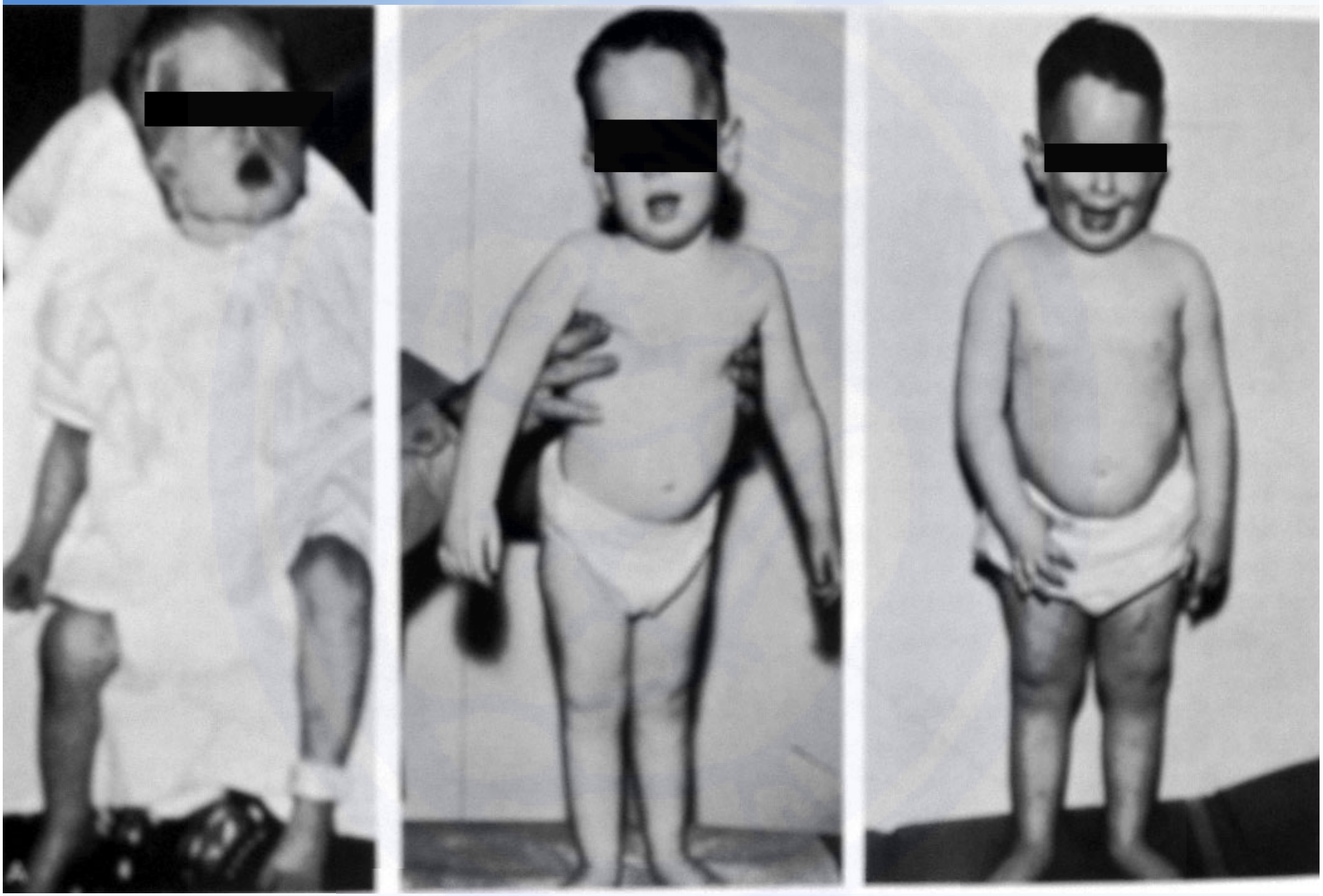
- Marfan syndrome
- Ehlers-Danlos syndrome

❑ *Congenital laxity of ligaments*

Cerebral (central) hypotonia

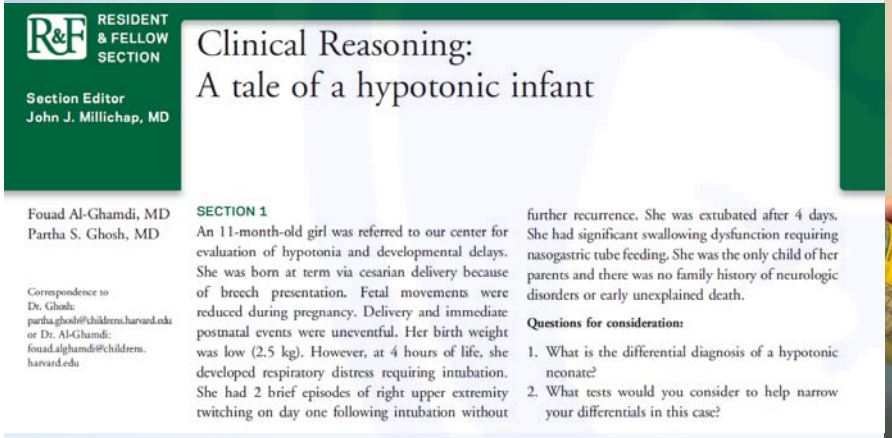
- Chromosomal disorders
- Other genetic defects
- Acute hemorrhagic and other brain injury
- Hypoxic/ischemic encephalopathy
- Chronic non-progressive encephalopathies
- Peroxisomal disorders (Zellweger syndrome, neonatal ALD, etc.)
- Metabolic defects
- Drug intoxication
- “Benign” congenital hypotonia





Prader-Willi Syndrome

Prader-Willi Syndrome



R&F RESIDENT & FELLOW SECTION

Section Editor
John J. Millichap, MD

Clinical Reasoning: A tale of a hypotonic infant

Fouad Al-Ghamdi, MD
Partha S. Ghosh, MD

Correspondence to
Dr. Ghosh:
partha.ghosh@childrens.harvard.edu
or Dr. Al-Ghamdi:
fouad.alghamdi@childrens.harvard.edu

SECTION 1

An 11-month-old girl was referred to our center for evaluation of hypotonia and developmental delays. She was born at term via cesarian delivery because of breech presentation. Fetal movements were reduced during pregnancy. Delivery and immediate postnatal events were uneventful. Her birth weight was low (2.5 kg). However, at 4 hours of life, she developed respiratory distress requiring intubation. She had 2 brief episodes of right upper extremity twitching on day one following intubation without further recurrence. She was extubated after 4 days. She had significant swallowing dysfunction requiring nasogastric tube feeding. She was the only child of her parents and there was no family history of neurologic disorders or early unexplained death.

Questions for consideration:

1. What is the differential diagnosis of a hypotonic neonate?
2. What tests would you consider to help narrow your differentials in this case?

Fouad Al-Ghamdi, MD
Partha S. Ghosh, MD

Neuromuscular diseases in the hypotonic infant and child

Anterior horn cell / Peripheral nerve

- Spinal muscular atrophies
- Hypoxic-ischemic myelopathy
- Traumatic myelopathy
- Neurogenic arthrogryposis
- Congenital neuropathies
  - Axonal
  - Hypomyelinating
  - Dejerine-Sotas
  - HSAN
  - Giant axonal neuropathy
  - Metabolic
  - Inflammatory

Neuromuscular junction

- Transient neonatal MG
- Congenital myasthenic syndromes
- Hypermagnesemia
- Aminoglycoside toxicity
- Infantile botulism

Muscle

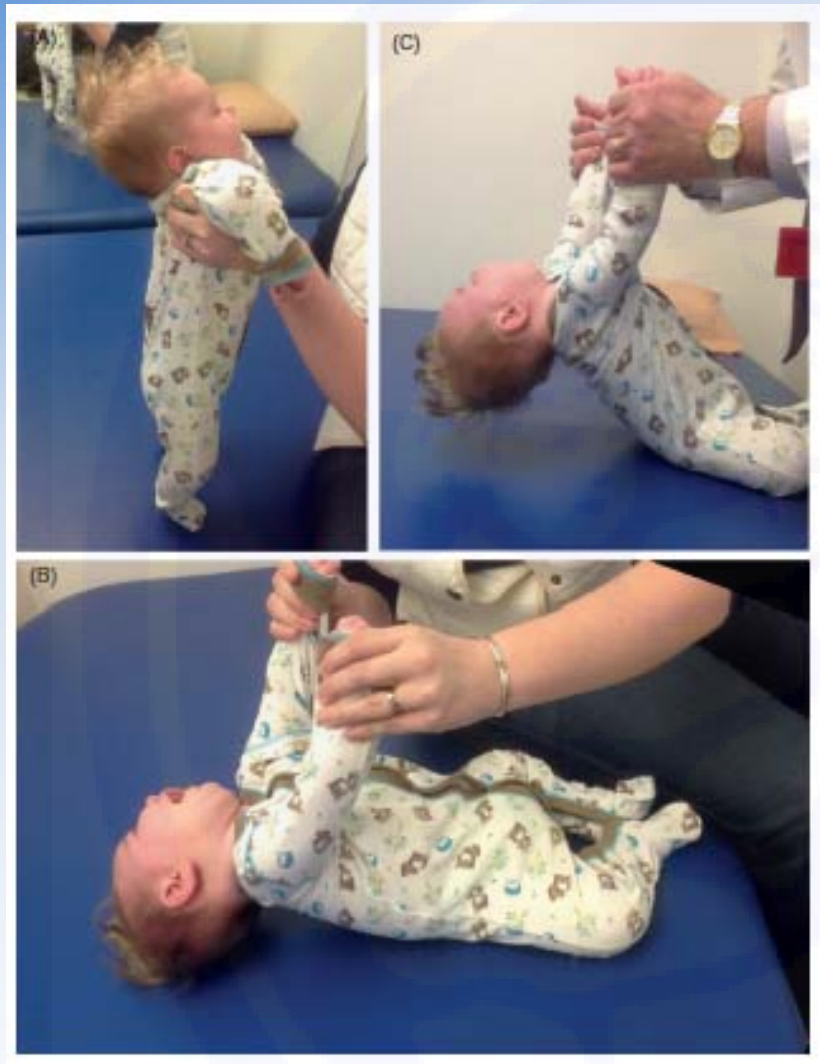
- Congenital muscular dystrophies
- Congenital myotonic dystrophy
- Infantile FSHD
- Congenital myopathies
- Metabolic myopathies
- Mitochondrial myopathies

Neuromuscular diseases in the hypotonic infant and child: *Anterior horn cell*

- Spinal muscular atrophies
  - SMN-associated SMA
  - Infantile SMA with respiratory distress
- Hypoxic-ischemic myelopathy
- Traumatic myelopathy
- Neurogenic arthrogryposis

Spinal muscular atrophy

- SMA, type I (severe)
  - Onset: birth to 6 months
  - Course: never sit unsupported
  - Death: usually < 2 years
- SMA, type II (intermediate)
  - Onset: < 18 months
  - Course: never stand or walk but sit at some time
  - Survival: 98.5% to age 5 years, 68.5% to age 25 years
- SMA, type III (mild)
  - Onset: > 18 months (IIIA <3 years, IIIB >3 years)
  - Course: able to stand and walk at some time
  - Survival: Almost normal life span



SMA

Neuromuscular diseases in the hypotonic infant and child: *Peripheral nerve*

Congenital neuropathies

- Axonal
- Hypomyelinating
- Dejerine-Sottas
- HSAN (Riley-Day syndrome)
- Giant axonal neuropathy
- Metabolic (e.g. lipid storage, FAO)
- Inflammatory

Neuromuscular diseases in the hypotonic infant and child: *Neuromuscular junction*

- Transient neonatal MG
- Congenital myasthenic syndromes
- Acquired autoimmune MG
- Hypermagnesemia
- Aminoglycoside toxicity
- Infantile botulism

Congenital myasthenic syndromes

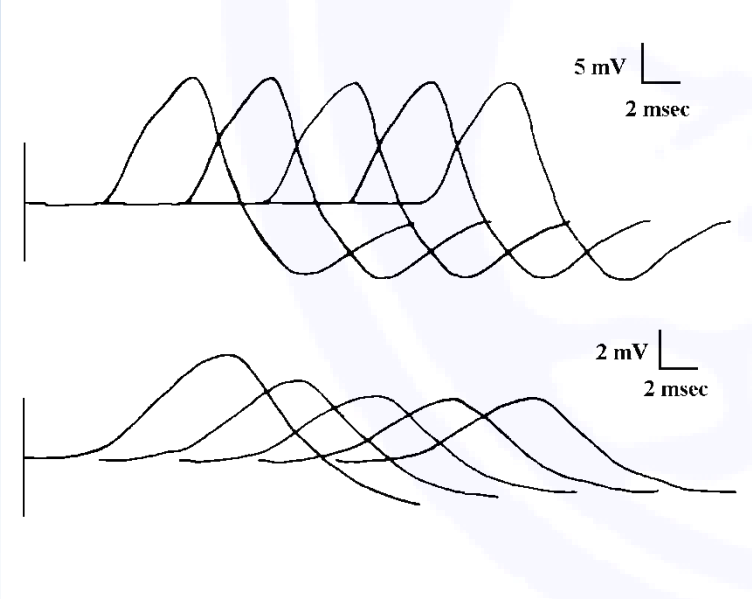
Defect	Inherit-ance	Clinical Features	Tensilon Test	Treatment
Presynaptic				
Familial infantile myasthenia with episodic apnea (ChAT mutations)	AR	Hypotonia Ptosis, apnea, no ophthalmoparesis Generalized weakness	+	AChE inhibitors
Postsynaptic or synaptic				
Congenital end-plate AChE deficiency	AR	Asymmetric ptosis Ophthalmoparesis Distal weakness Delayed pupillary constriction to light	–	No response to AChE inhibitors
Classic slow channel syndrome	AD	Ophthalmoparesis Fluctuating ptosis Head and wrist extensor weakness	–	No response to AChE inhibitors
Congenital AChR deficiency (rapsyn or ε-subunit mutations)	AR	Hypotonia, ptosis Ophthalmoplegia (ε-subunit) Strabismus (rapsyn) Respiratory failure (rapsyn) Feeding difficulties Arthrogryposis (rapsyn)	+	AChE inhibitors
Dok-7 myasthenia	AR	Proximal weakness Ptosis Facial weakness Respiratory failure	–	Poor response to AchE inhibitors

Infantile botulism

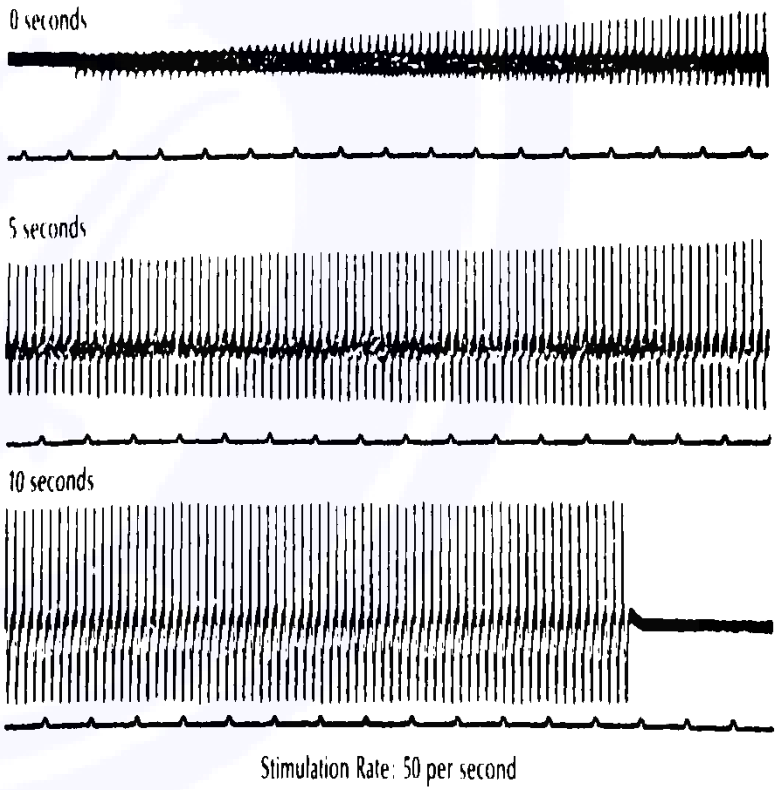
- Age: 10 days to 12 months (median: 10 weeks)
- Acute weakness, hypotonia, dysphagia, weak cry, respiratory failure, constipation
- Ptosis, ophthalmoplegia, mydriasis
- EMG/NCS: decrement, facilitation (125-3,000%) plus myopathic potentials
- C. botulinum toxin in stool
- Rx: Supportive, botulinum immune globulin (BIG)

Infantile botulism

- Decrement at 2-5 Hz



- Facilitation at 20-50 Hz



Neuromuscular diseases of the hypotonic infant and child: *Muscle*

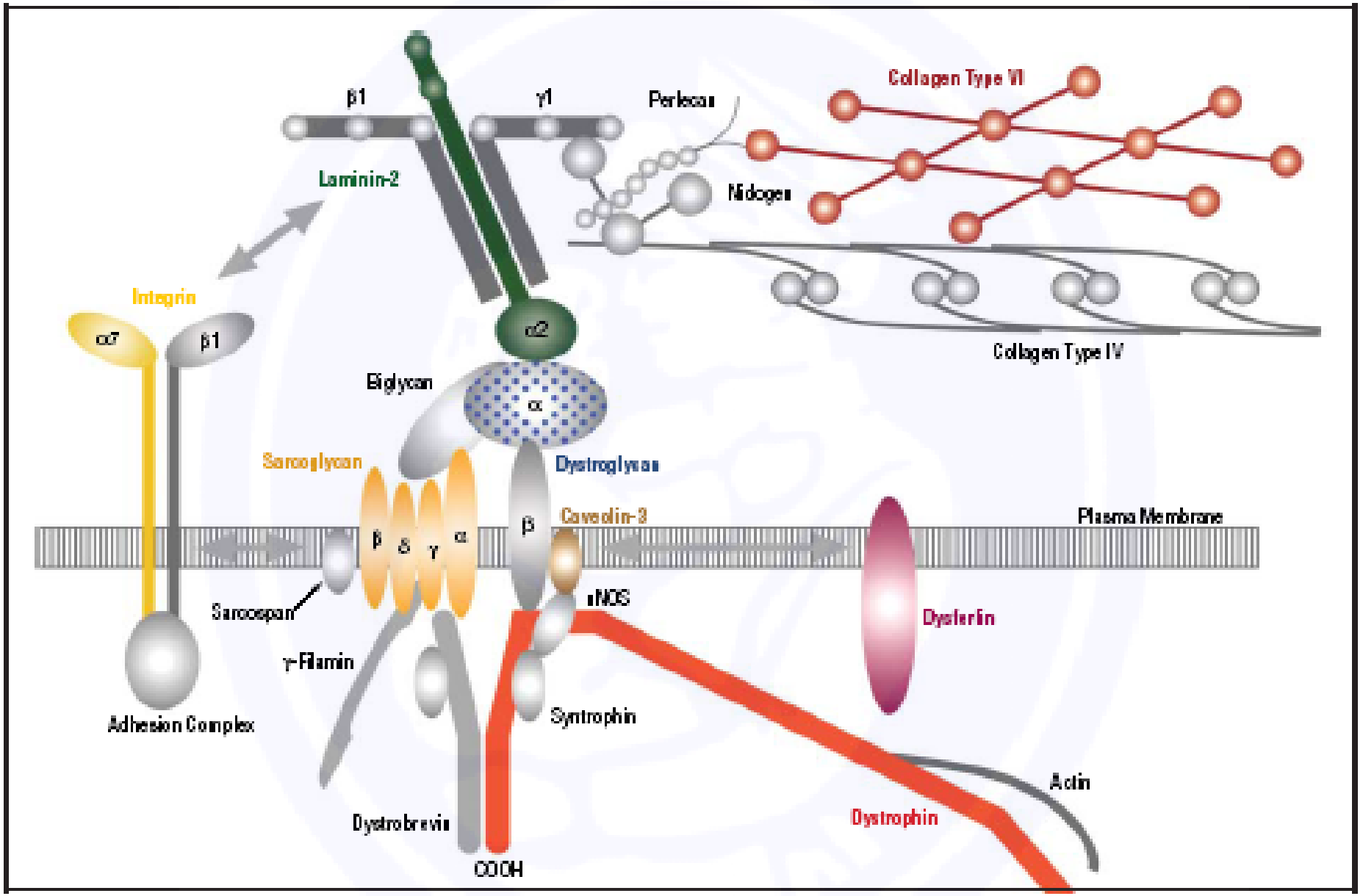
- Congenital muscular dystrophies
- Congenital myotonic dystrophy
- Infantile FSHD
- Congenital myopathies
- Metabolic myopathies
  - Mitochondrial myopathies
  - Others

Muscle disorders in the hypotonic infant

- **Classical CMD**
  - Merosin-deficient CMD
    - Primary merosin deficiency
    - Secondary merosin deficiency
  - Merosin-positive CMD
    - Classical CMD without distinguishing features
    - Rigid spine syndrome
    - CMD with distal hyperextensibility (Ullrich type)
    - CMD with mental retardation or sensory abnormalities
- **CMDs with CNS abnormalities**
  - Fukuyama muscular dystrophy
  - Muscle-eye-brain disease
  - Walker-Warburg syndrome

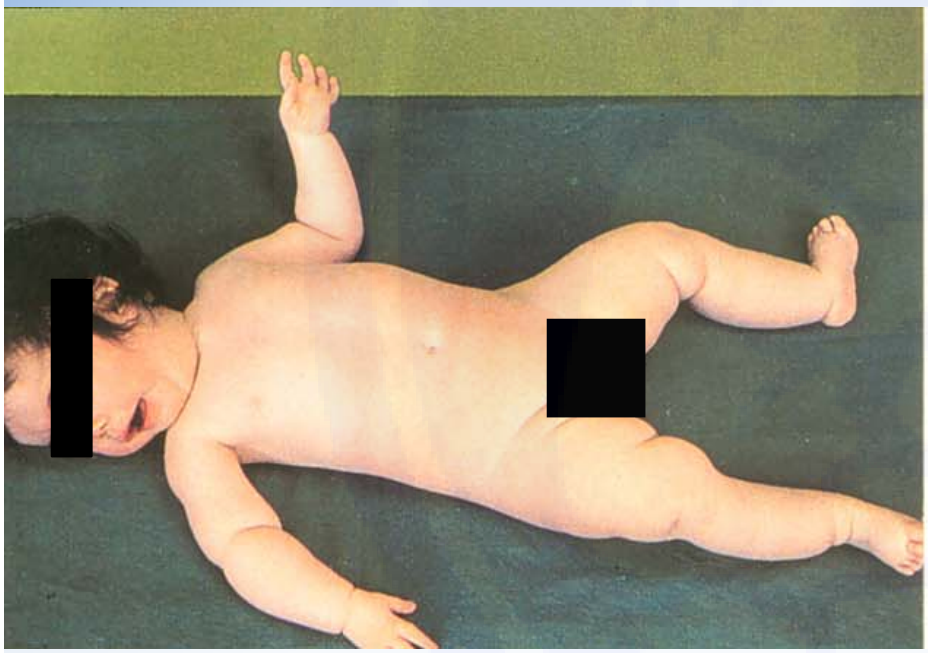
Genetic loci for congenital muscular dystrophy (CMD): Classical CMD

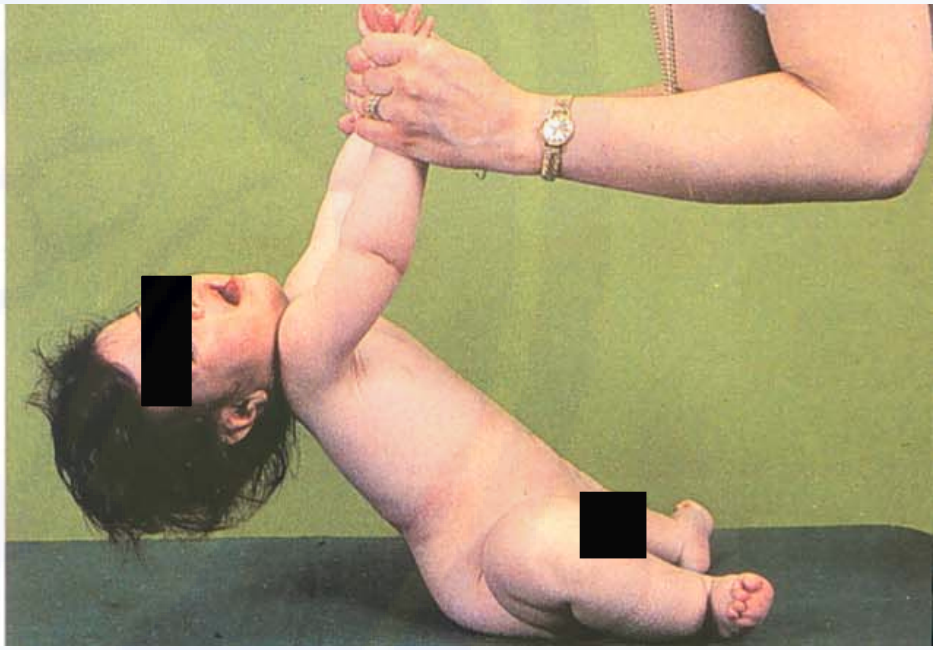
Disease	Inheritance	Gene location	Symbol (Gene Product)
Primary merosin deficiency (MDC1A)	AR	6q22-q23	*LAMA2* (laminin α2 chain of merosin)
Secondary merosin deficiency (MDC1B)	AR	1q42	?
Secondary merosin deficiency (MDC1C)	AR	19q13.3	*FKRP* (fukutin-related protein)
Rigid spine syndrome (RSMD)	AR	1p35-p36	*RSMD1* (selenoprotein N)
Ullrich muscular dystrophy (UCMD)	AR	21q22.3	*COL6A1* (collagen VI α1 chain)
	AR	21q.22.3	*COL6A2* (collagen VI α2 chain)
	AR	2q37	*COL6A3* (collagen VI α3 chain)
Integrin α7 deficiency	AR	12q13	Integrin α7

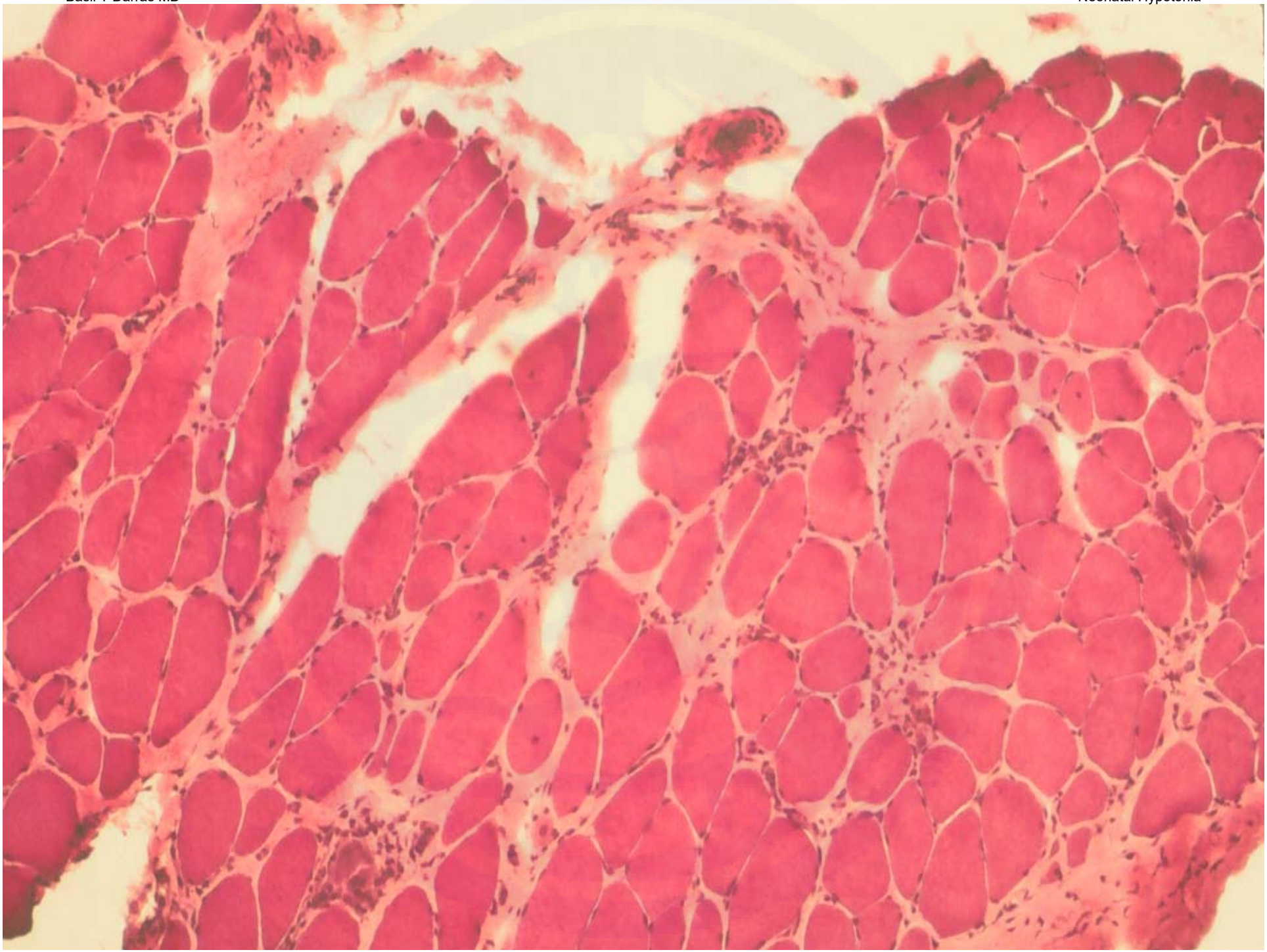


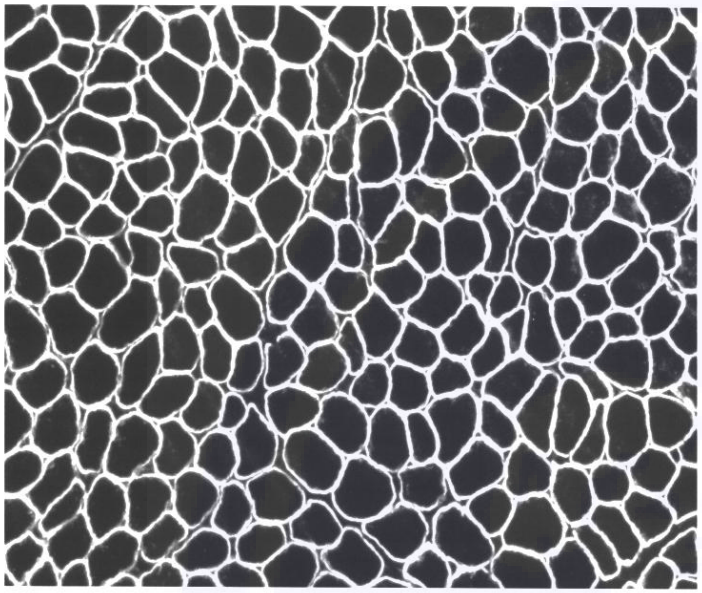
Schematic representation of the dystrophin-associated proteins and other sarcolemmal and extracellular proteins relevant to muscular dystrophy. Proteins for which mutations in the corresponding genes have been shown to cause muscular dystrophies are shown in color. α-Dystroglycan (dotted pattern) can be indirectly involved via alterations of its O-linked glycosylation. nNOS indicates neuronal nitric oxide synthase; COOH, carboxy terminus; and NH_2, amino terminus. Adapted with permission from *Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach*.[22] Copyright 2003, Elsevier.

Merosin-deficient CMD (MDC1A)

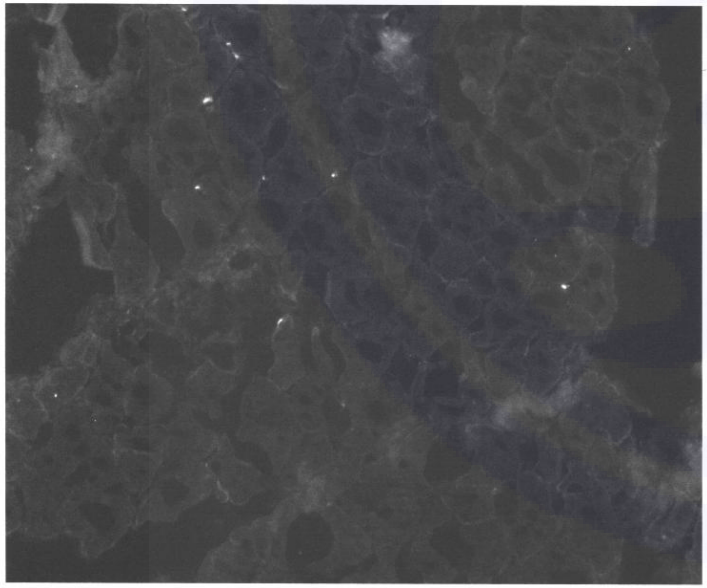


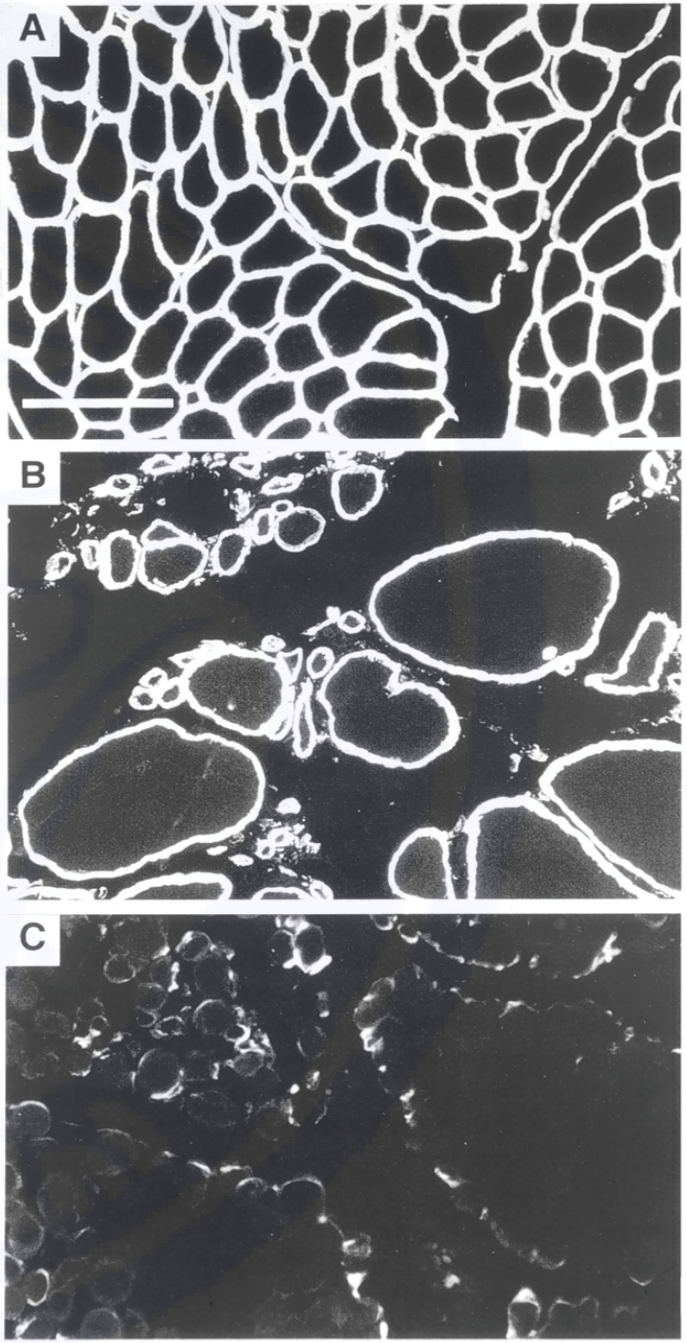






MDC1A

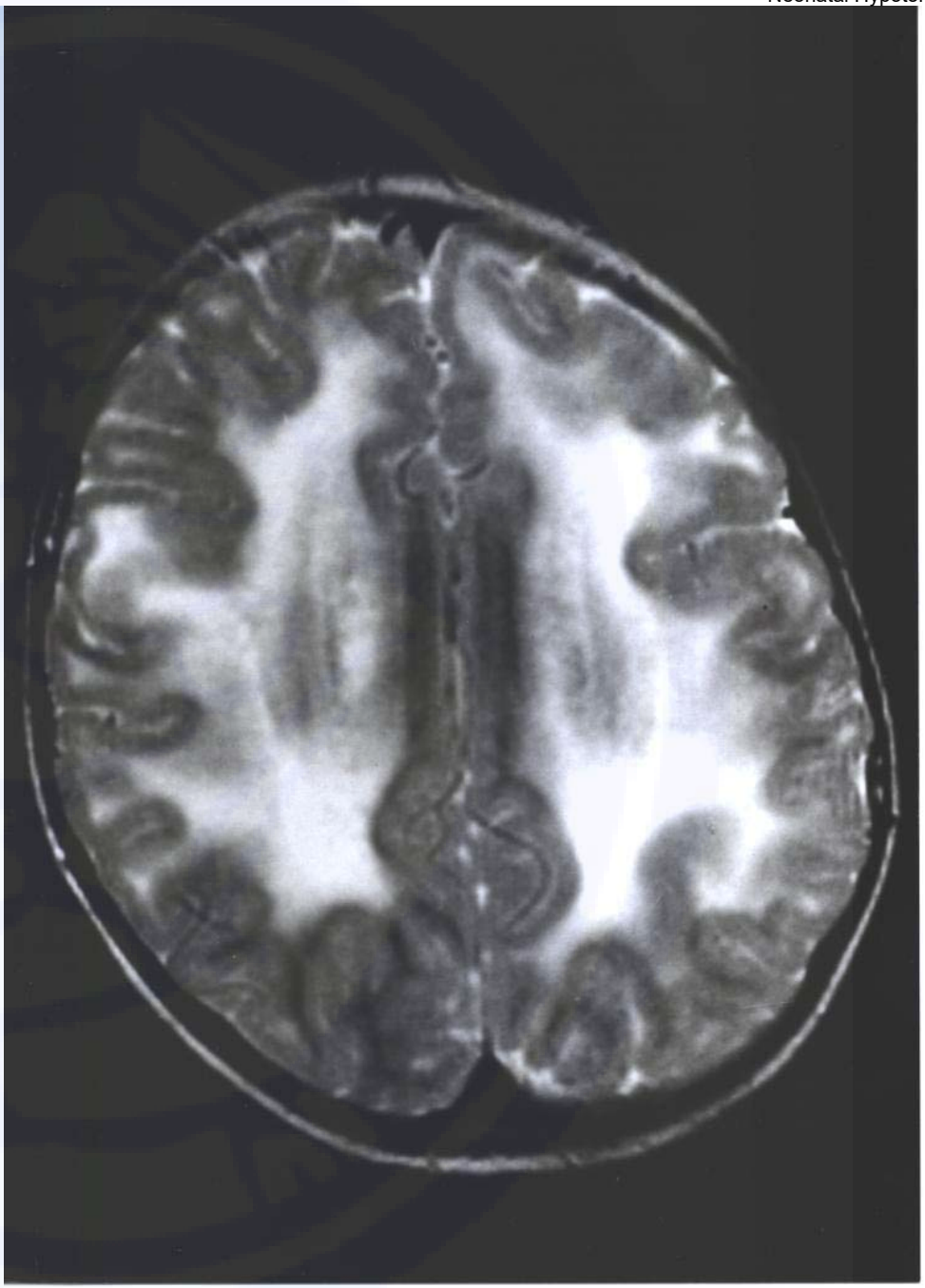




MDC1A

Brain MRI

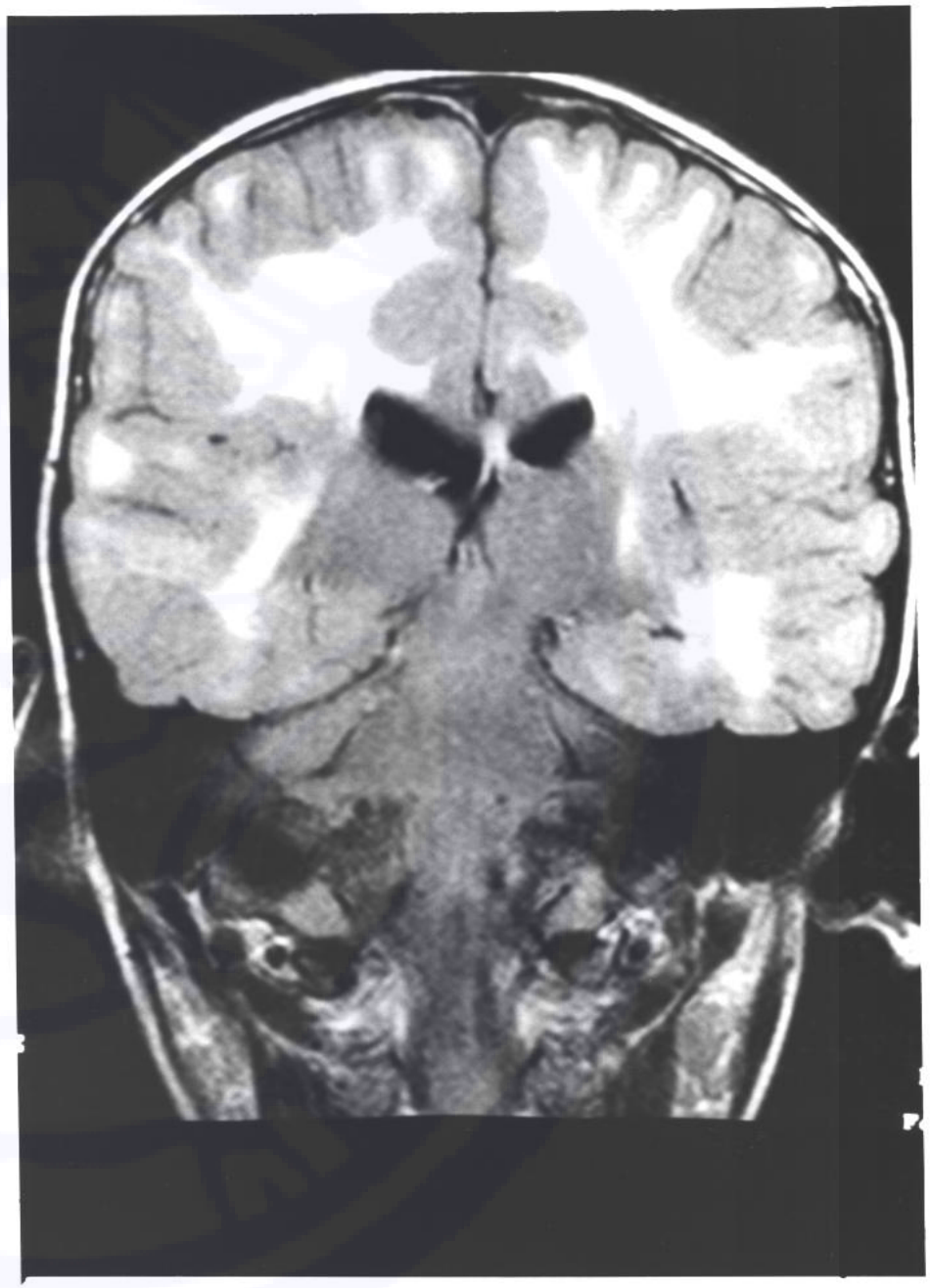
Merosin-deficient congenital muscular dystrophy



MDC1A

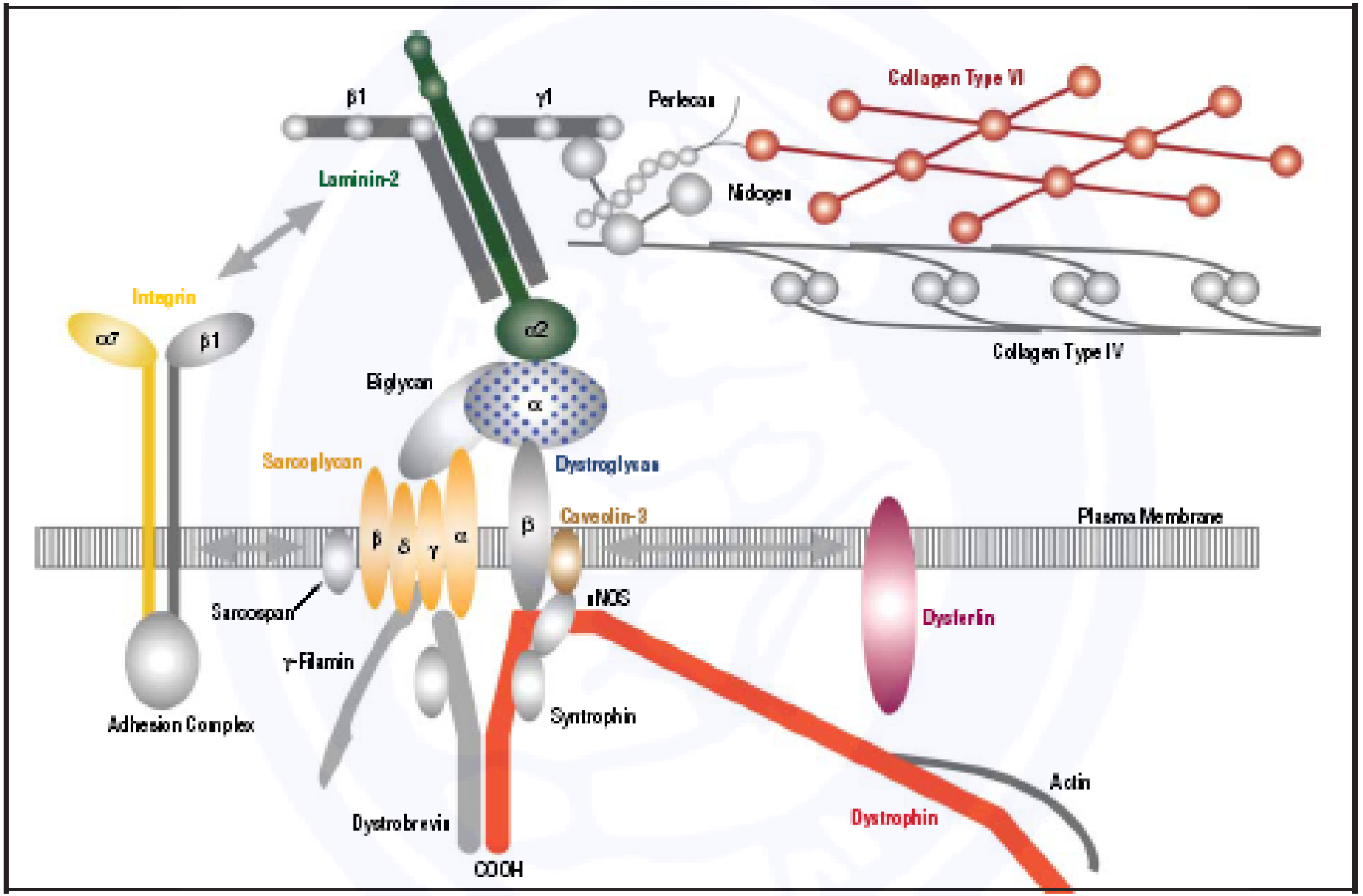
Brain MRI

Merosin-deficient congenital muscular dystrophy



Genetic loci for congenital muscular dystrophy (CMD): Classical CMD

Disease	Inheritance	Gene location	Symbol (Gene Product)
Primary merosin deficiency (MDC1A)	AR	6q22-q23	*LAMA2* (laminin α2 chain of merosin)
Secondary merosin deficiency (MDC1B)	AR	1q42	?
Secondary merosin deficiency (MDC1C)	AR	19q13.3	*FKRP* (fukutin-related protein)
Rigid spine syndrome (RSMD)	AR	1p35-p36	*RSMD1* (selenoprotein N)
Ullrich muscular dystrophy (UCMD)	AR	21q22.3	*COL6A1* (collagen VI α1 chain)
	AR	21q.22.3	*COL6A2* (collagen VI α2 chain)
	AR	2q37	*COL6A3* (collagen VI α3 chain)
Integrin α7 deficiency	AR	12q13	Integrin α7



Schematic representation of the dystrophin-associated proteins and other sarcolemmal and extracellular proteins relevant to muscular dystrophy. Proteins for which mutations in the corresponding genes have been shown to cause muscular dystrophies are shown in color. α-Dystroglycan (dotted pattern) can be indirectly involved via alterations of its O-linked glycosylation. nNOS indicates neuronal nitric oxide synthase; COOH, carboxy terminus; and NH_2, amino terminus. Adapted with permission from *Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach*.[22] Copyright 2003, Elsevier.

Characteristic clinical features of congenital muscular dystrophies with structural CNS abnormalities

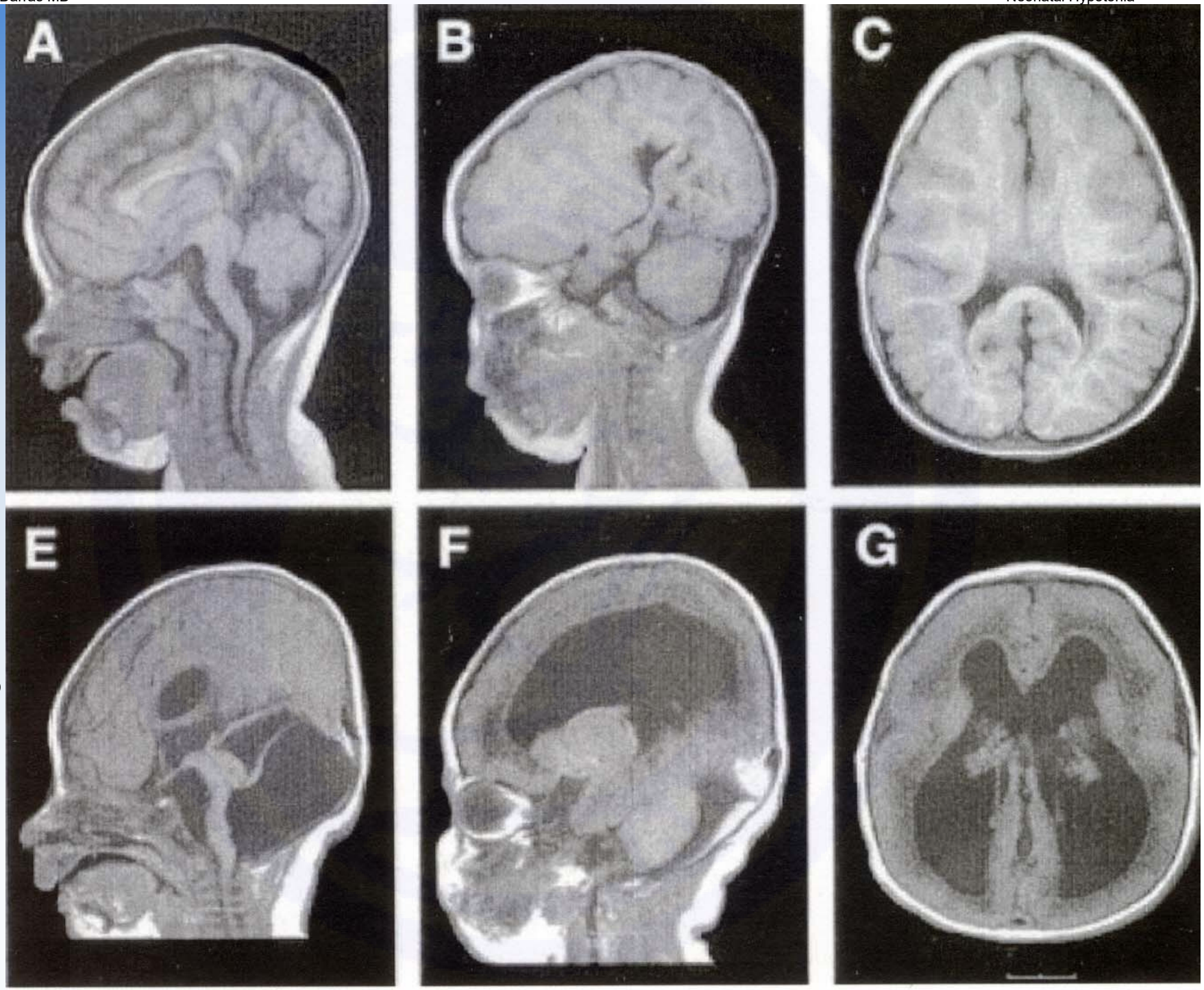
	WWS	MEB	FCMD
Ocular	Severe malformations, including malformation of anterior chamber and persistent primary vitreous	Progressive myopia and retinal degeneration associated with giant VEPs	Simple myopia without structural changes
Brain	Lissencephaly II (cobblestone) with variable gyral malformation, diffuse WM abnormality, ventricular dilatation	Brain stem characteristically flat Cobblestone cortex	Brain stem normal Pachygyria Microgyria Heterotopias
Clinical course	Very severe, and many patients die in early infancy	Patients survive beyond age 3 years	Less severe

Genetic loci for congenital muscular dystrophy (CMD): *CMD with CNS abnormalities*

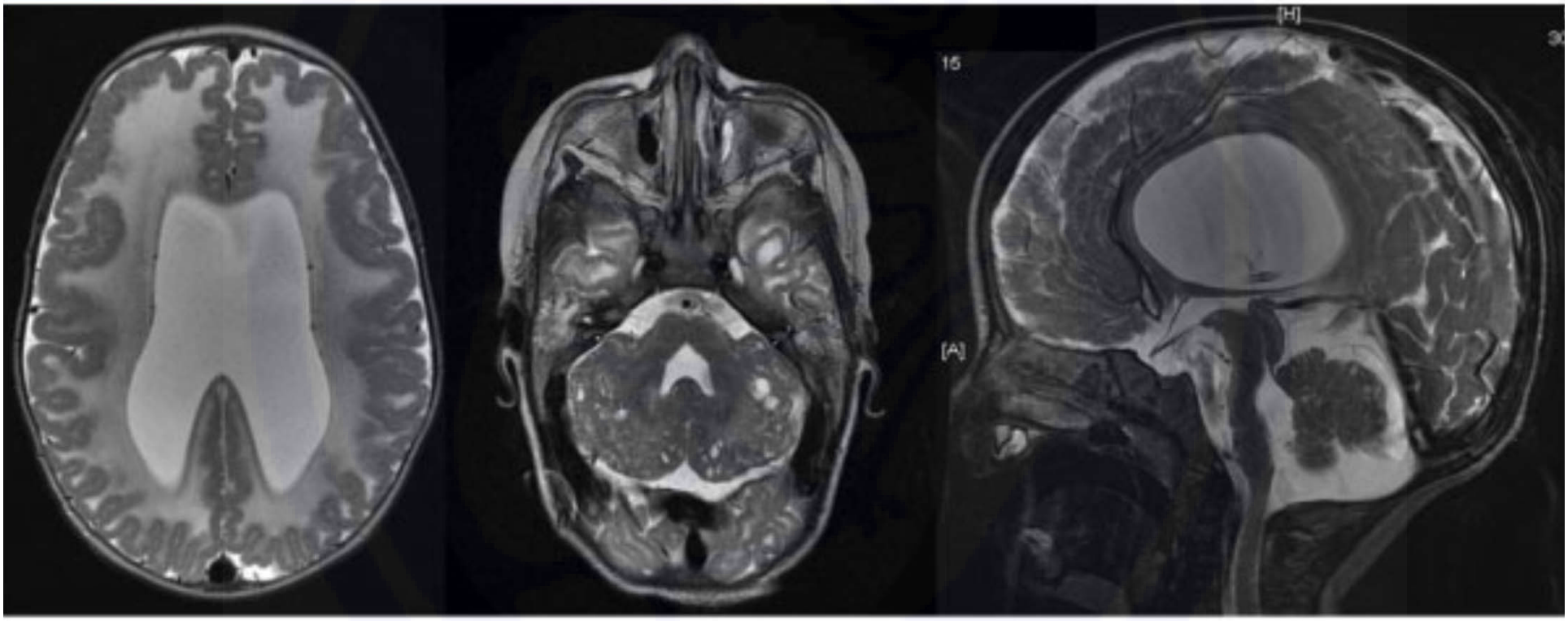
Disease	Inheritance	Gene location	Symbol (Gene Product)
Fukumaya CMD	AR	9q31-33	*FCMD* (fukutin)
Muscle-eye-brain disease	AR	1p32-p34	*POMGnT1* (glycosyltransferase) *POMT1*, *POMT2*, *FKRP* (fukutin-related protein)
Walker-Warburg syndrome	AR	9q34.1	*POMT1* (mannosyltransferase)
		9q31-33	*FCMD* (fukutin)
		19q13.3	*FKRP* (fukutin-related protein)
		14q24.3	*POMT2* (mannosyltransferase)
LARGE-related CMD (MDC1D)	AR	22q12.3	LARGE (putative glycosyltransferase)

MEB

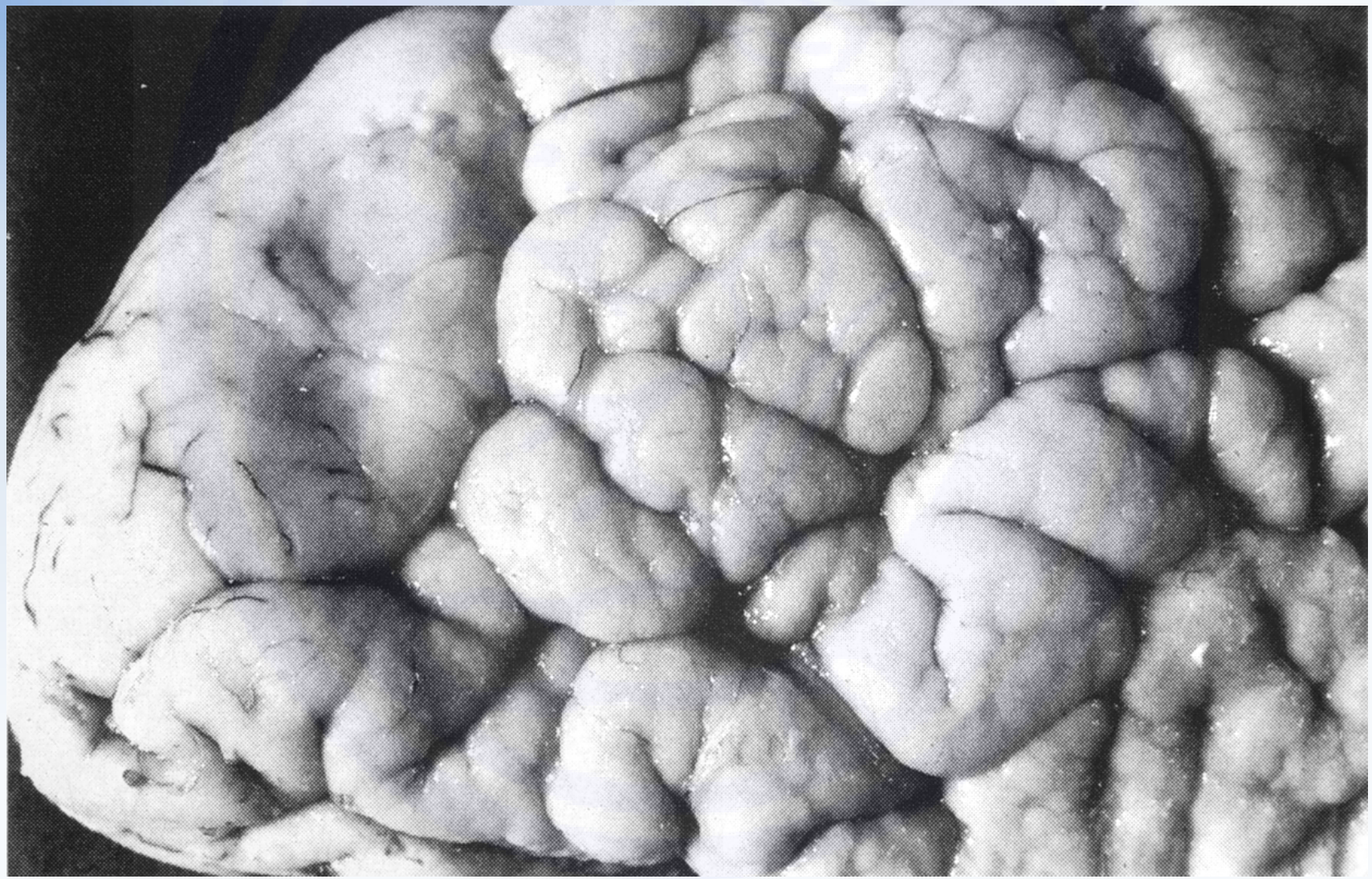
WWS



Muscle-eye-brain disease (POMGnT1)



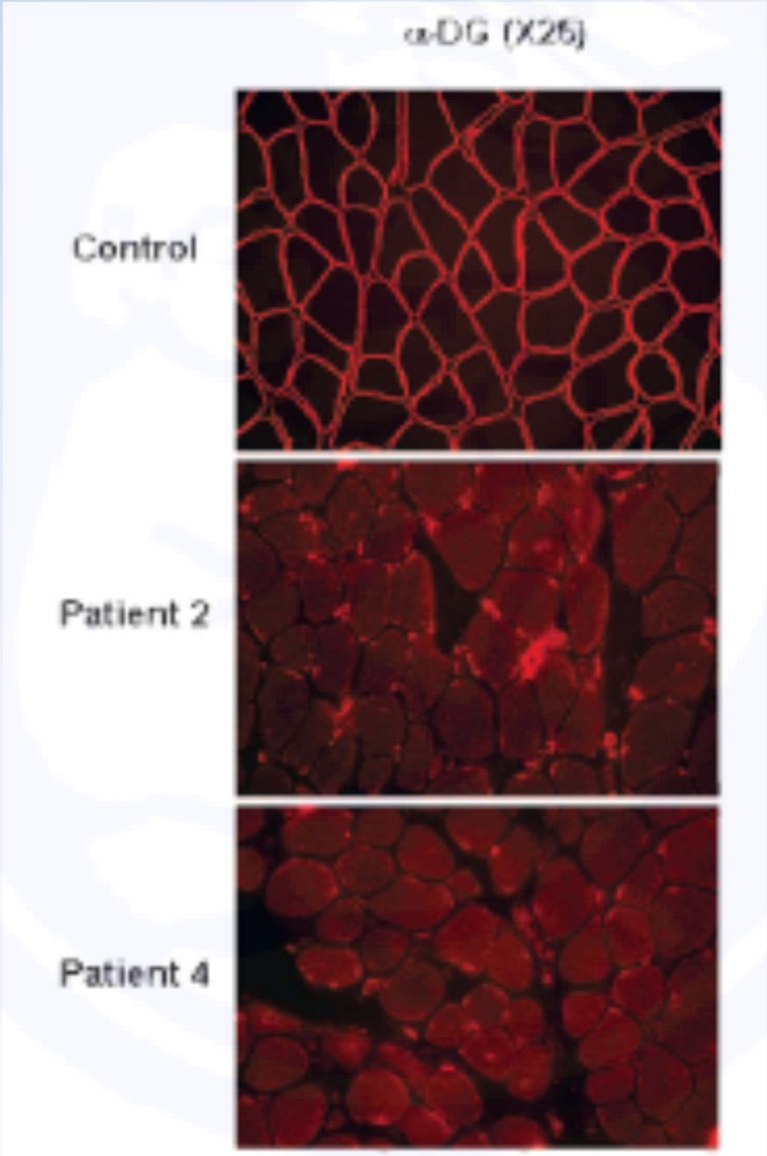
Muscle-eye-brain disease



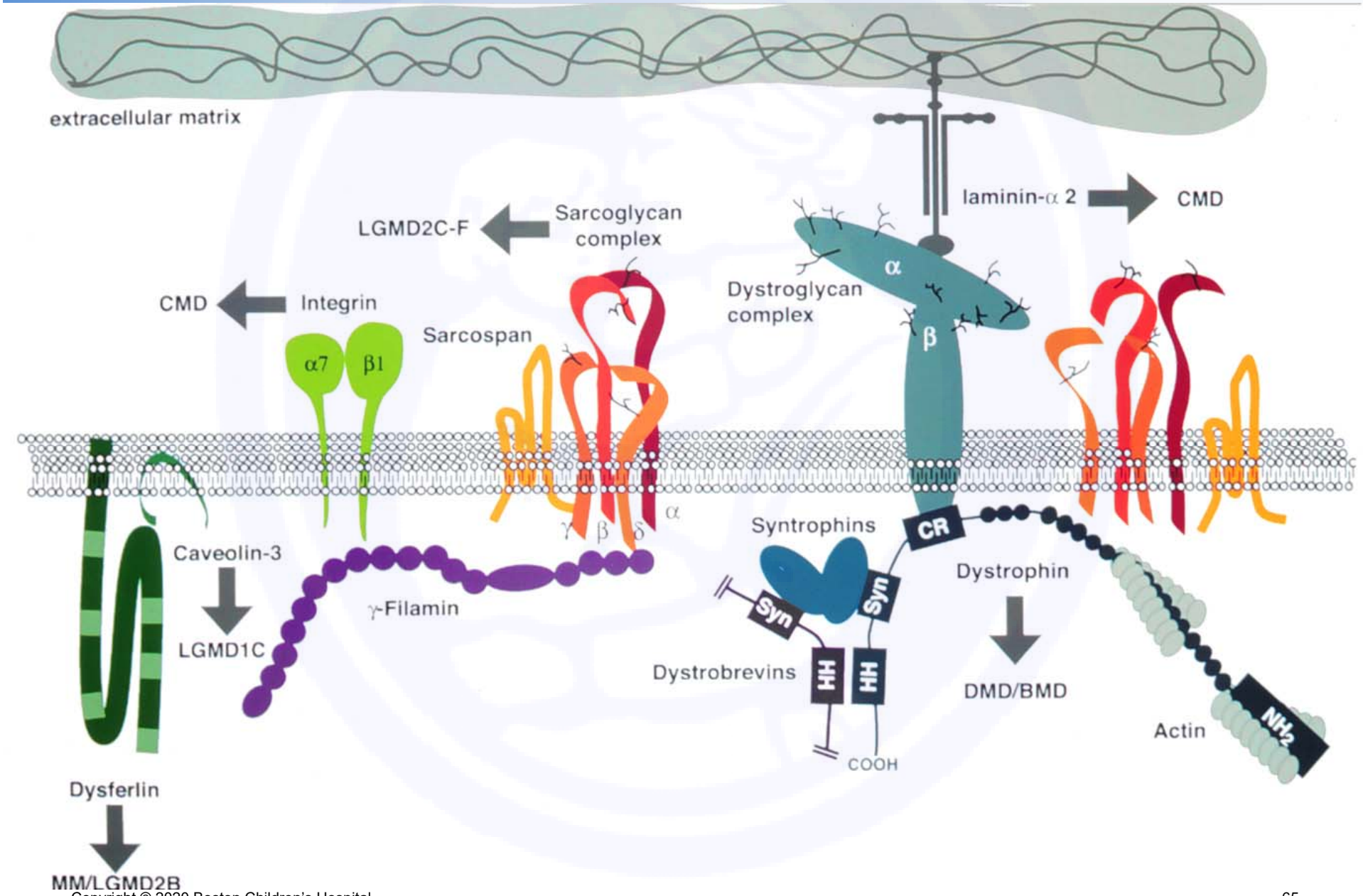
WWS, MEB, FCMD, MDC1C, MDC1D

- Deficient a-dystroglycan in the basal lamina of skeletal muscles with VIA4-1 monoclonal antibody
- Normal a-dystroglycan staining using a polyclonal antibody
- VIA4-1 directed against the glycan epitope(s) of the a-dystroglycan molecule
- a-dystroglycan is underglycosylated
- Laminin-a2 staining may be decreased
- Fukutin: secreted glycosyltransferase?
- FKRP, *Large*: putative glycosyltransferases
- POMT1, 2, POMGnT1: glycosyltransferases

POMT2 mutations: IF analysis of muscle biopsies



DAP complex

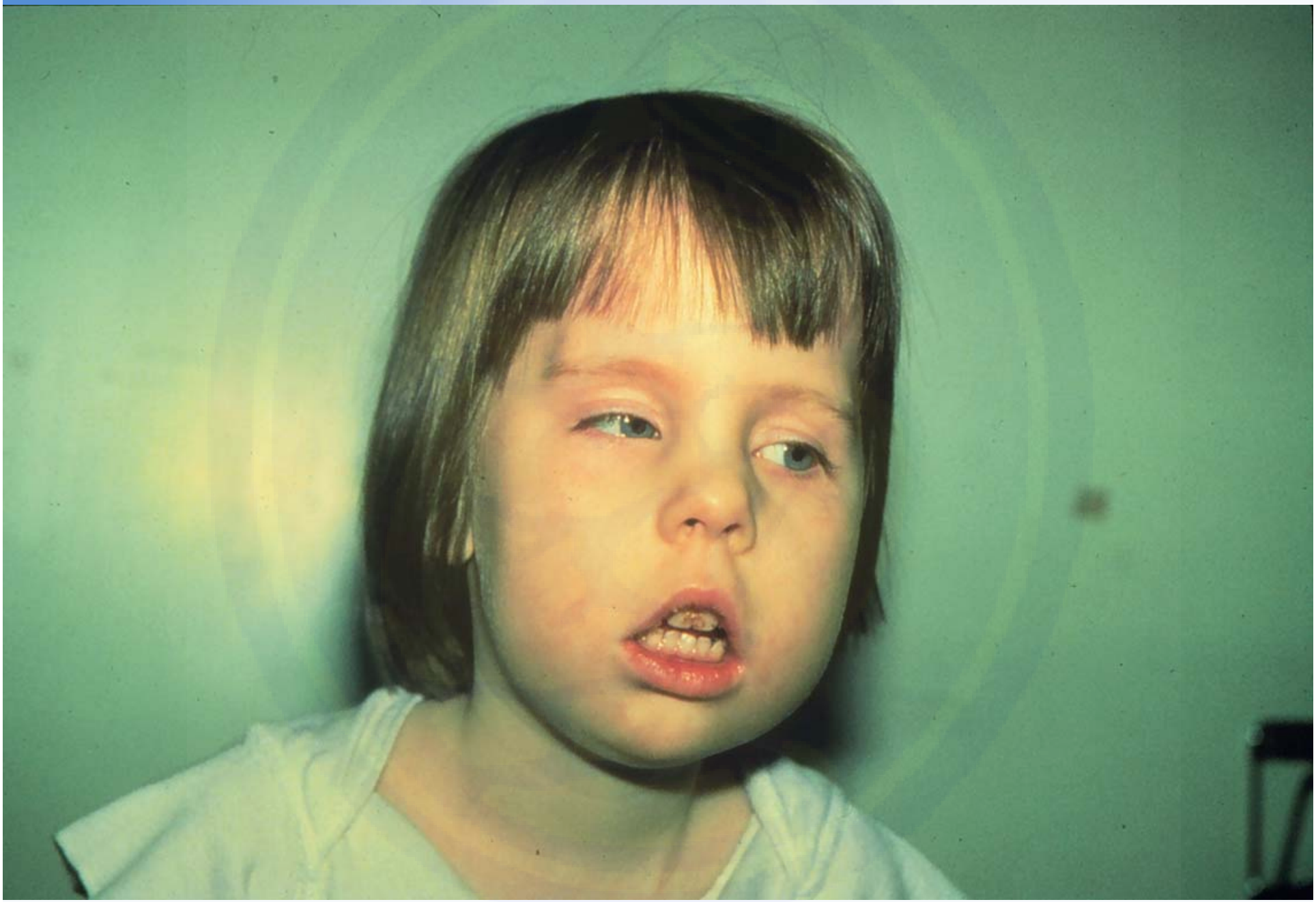


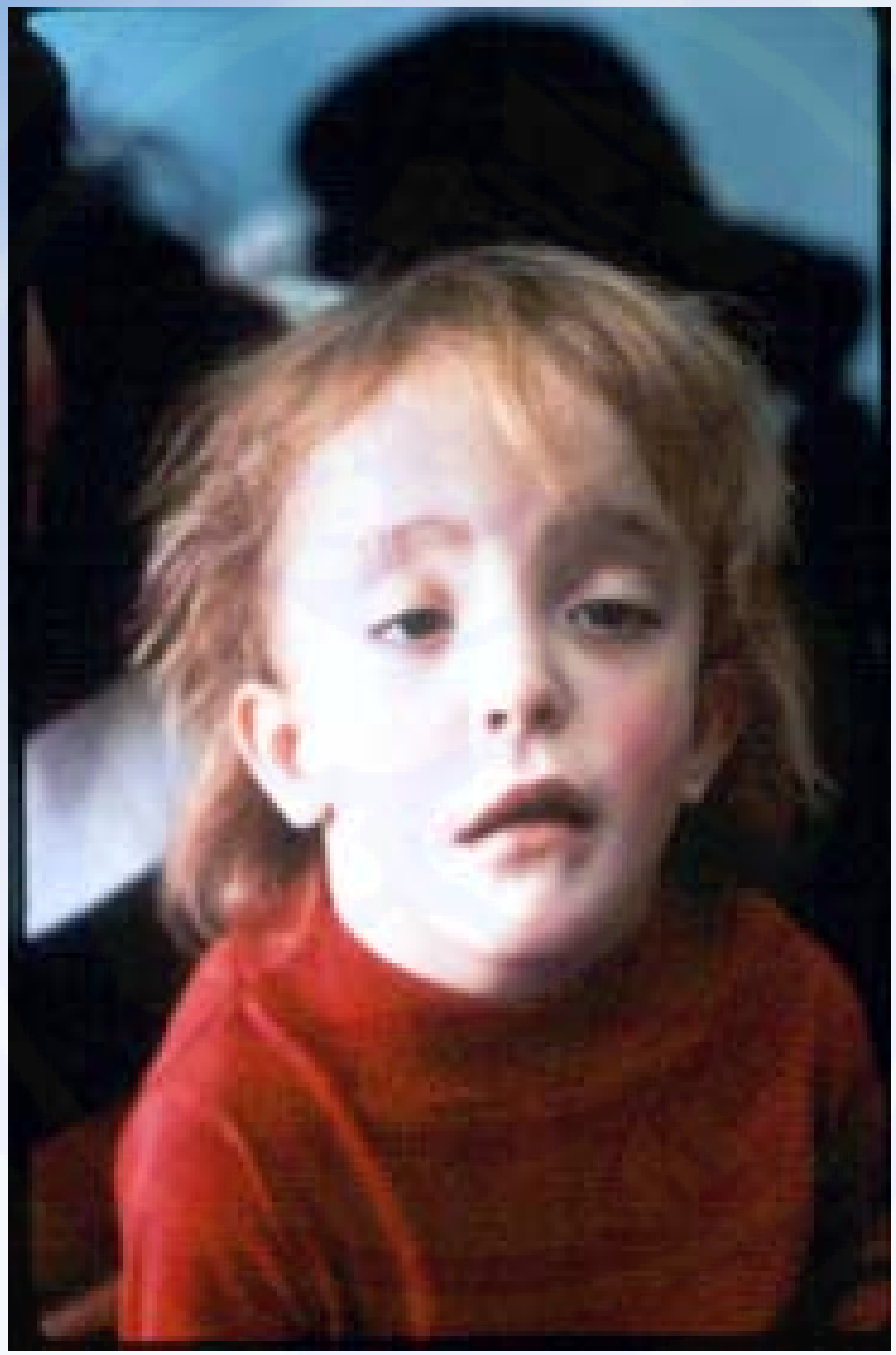
Myotonic dystrophy syndromes

- Myotonic dystrophy, type 1 (DM1)

- Congenital myotonic dystrophy (DM1)

- Myotonic myopathy, type 2 (DM2, PROMM)





DM1

Myotonic dystrophy, type 1 (DM1)

Genetics

(CTG)n repeat expansion:

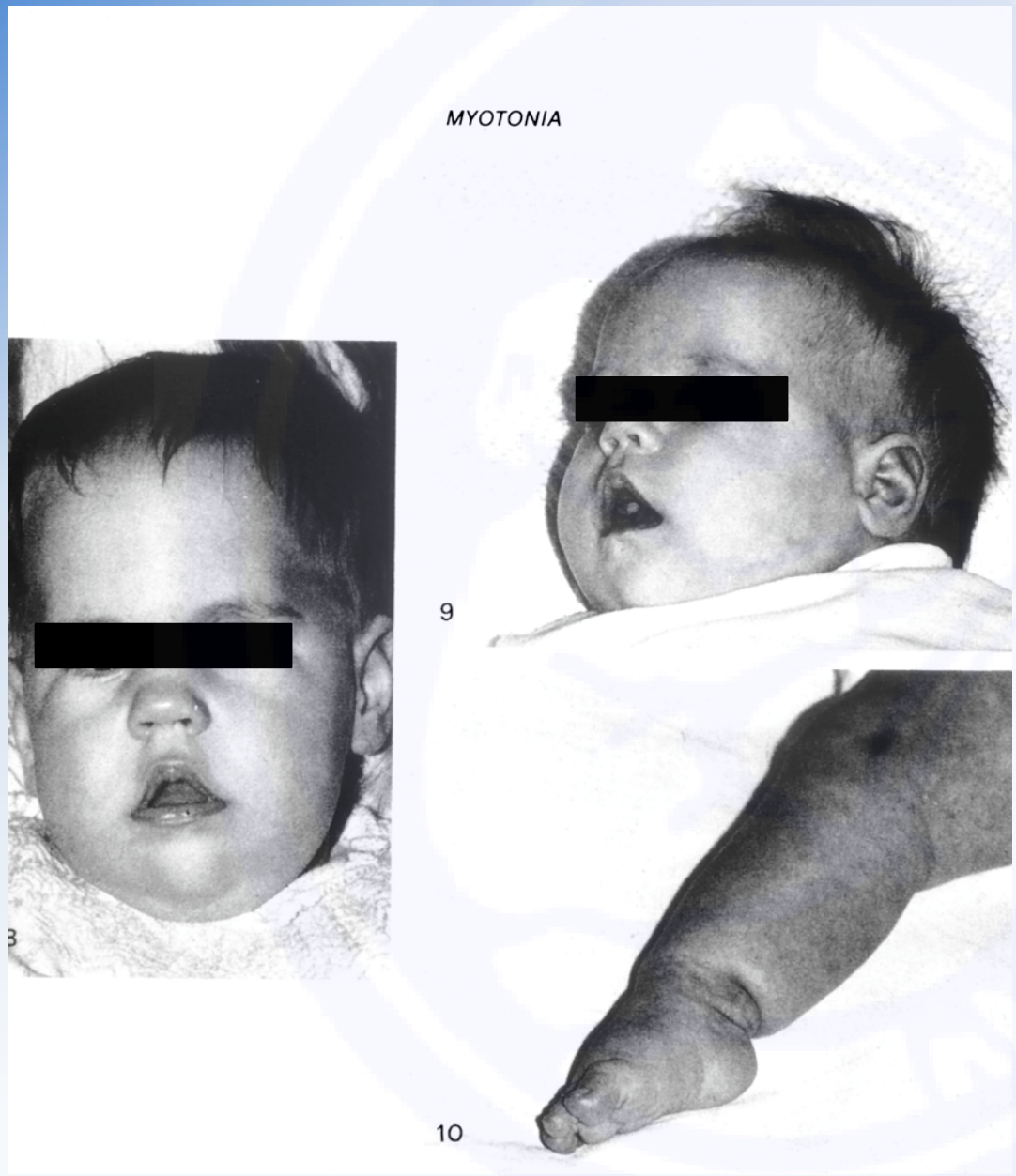
- Normal : 4 – 37 copies
- Premutation : 38 – 49 copies
- Protomutation : 50 – 80 copies
- Full-mutation : > 80 copies

Phenotype

- Minimal : 50 – 80 copies
- Classical : 100 – 750 copies
- ❑ Congenital : > 750 copies

Congenital myotonic dystrophy (DM1)

- Inheritance: 15%-25% of offspring of affected myotonic dystrophy mothers
- Features: hypotonia, poor feeding, facial weakness, club feet, MR
- Labs:
  - CK level: usually normal
  - EMG: often no myotonia
  - Large CTG repeat expansion



Congenital DM1

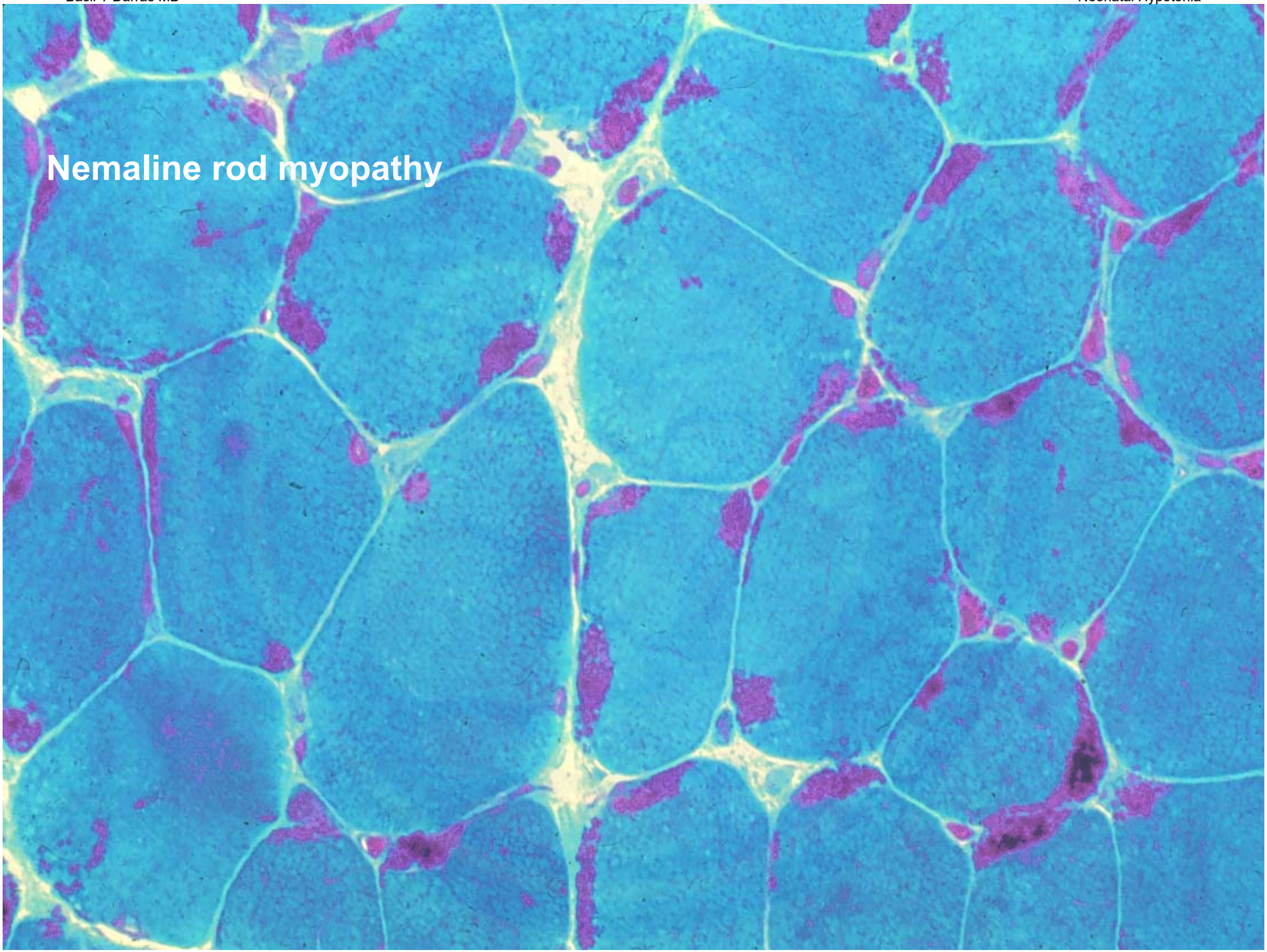
Congenital myopathies

- Hypotonia, weakness
- Dysmorphic features
- Normal or slightly elevated CK
- Normal or myopathic EMG
- Typical/diagnostic muscle biopsy
- DNA testing may be available
- Check genetests.org

Muscle disorders in the hypotonic infant

Congenital myopathies

- Nemaline myopathy
- Central core disease
- Centronuclear/myotubular myopathy
- Congenital fiber type disproportion
- Minicore disease
- Other congenital myopathies



Congenital myopathies

- Hypotonia, weakness
- Dysmorphic features
- Normal or slightly elevated CK
- Normal or myopathic EMG
- Typical/diagnostic muscle biopsy
- DNA testing may be available
- Check genetests.org

Congenital myopathies

Disease	Genes	Proteins	Onset
Centronuclear myopathy, X-linked (myotubular myopathy	*MTM1*	Myotubularin	Prenatal – congenital
Centronuclear myopathy, adult	*DNM2*	Dynamin 2	Infancy, 2nd – 3rd decade
Nemaline myopathy	*ACTA1* *NEM2* *TPM3* *TPM2* *TNNT1* *CFL2*	α-Actin Nebulin α-Tropomyosin β-Tropomyosin Troponin T type I Cofilin 2	Infancy – adulthood
Central core, classical	*RYR1*	Ryanodine receptor	Infancy
Congenital fiber-type disproportion	*ACTA1* *TPM3* *SEPN1*	α-Actin α-Tropomyosin Selenoprotein	1st year
Multiminicore disease	*SEPN1* *RYR1*	Selenoprotein	Infancy – early childhood

Muscle disorders in the hypotonic infant

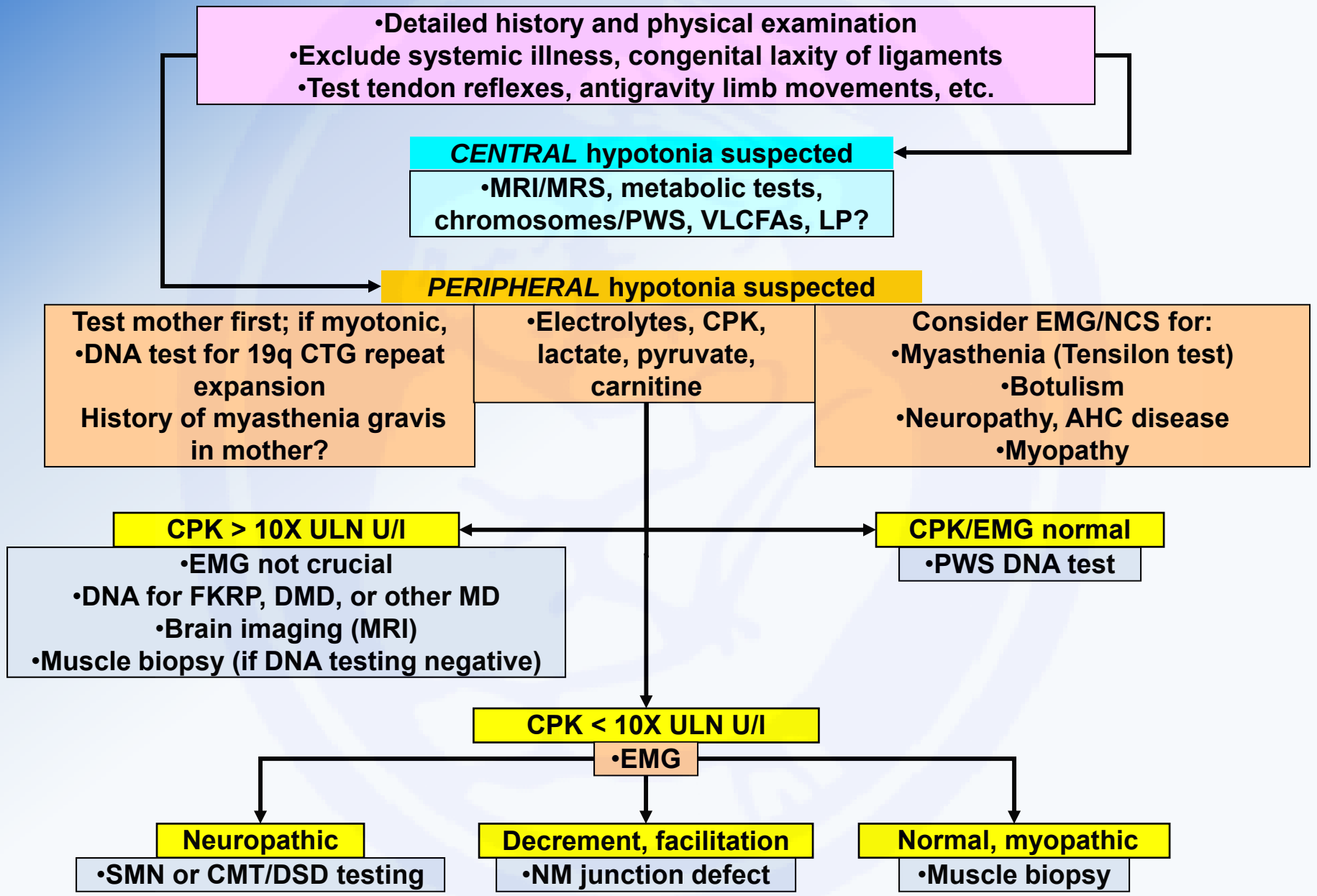
Metabolic myopathies

- Acid maltase deficiency (Pompe D.)
- Mitochondrial myopathies
  - Carnitine deficiency
  - Cytochrome c oxidase/ETC defects
  - mtDNA depletion
  - Fatty acid oxidation defects
- Non-lysosomal glycogenoses

Neonatal hypotonia

- McGill University Study (Richer et al, Pediatr Neurol 25(1):32-37, 2001): 11-year study
- Central: 33 patients (66%)
- Peripheral: 17 patients (34%)
- Most common diagnoses:
  - HIE (n=13)
  - PWS (n=6)
  - Myotonic dystrophy (n=6)
  - Other muscle disorders (n=6)
  - Chromosomal disorders (n=4)
  - Peripheral nerve disorders (n=3)

Approach to Hypotonia



Thank you