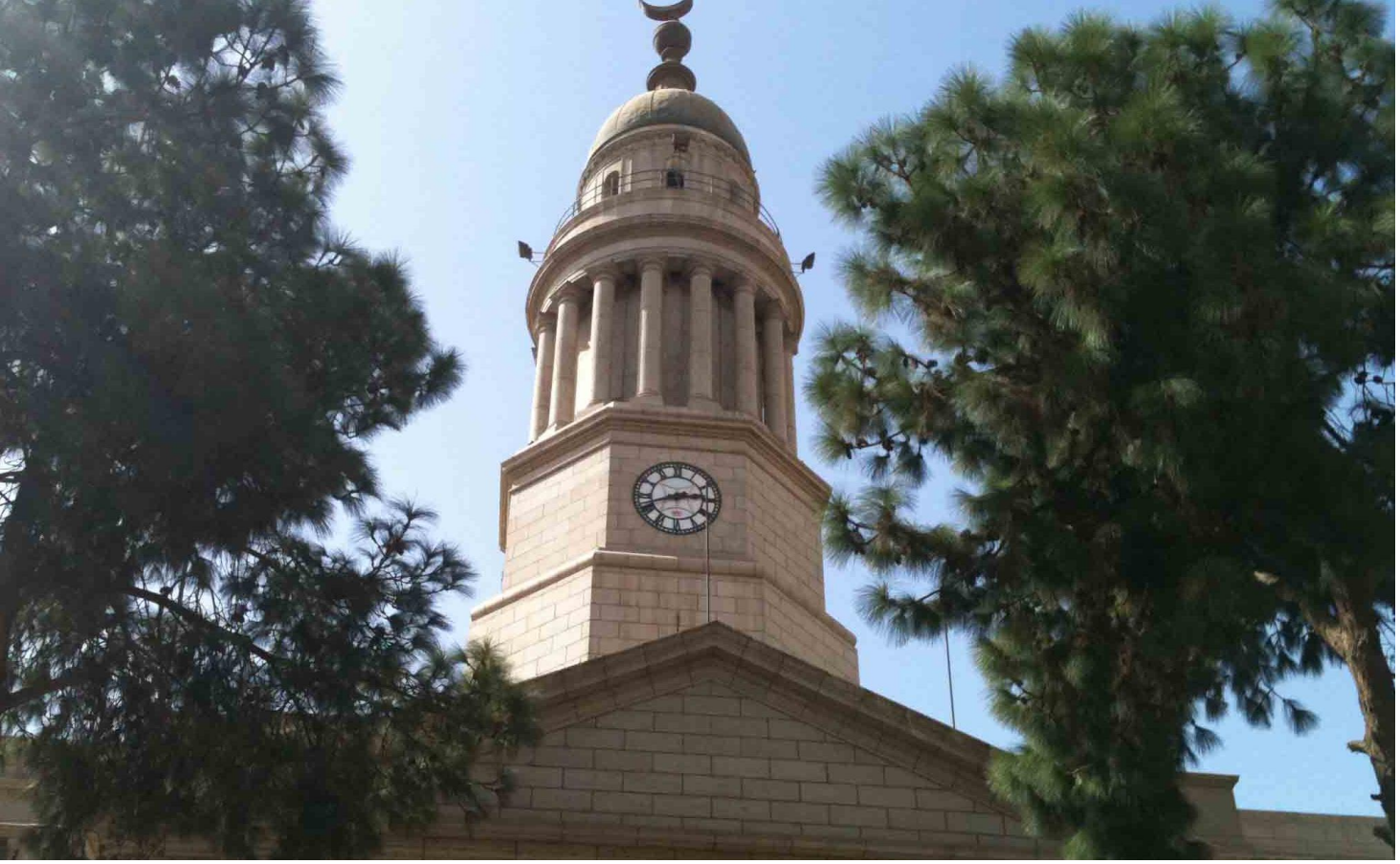

FLOPPY INFANT

Amr Hassan MD,FEBN

Associate Professor of Neurology - Cairo University

AGENDA

- Definition
- Clinical examination
- Differential diagnosis
- Investigations

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Floppy Infant

Floppy infant refers to those children presenting with generalized hypotonia, most often arising out of an insult incurred during fetal or neonatal period.

AGENDA

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Neonatal Hypotonia

Prenatal risk factors:

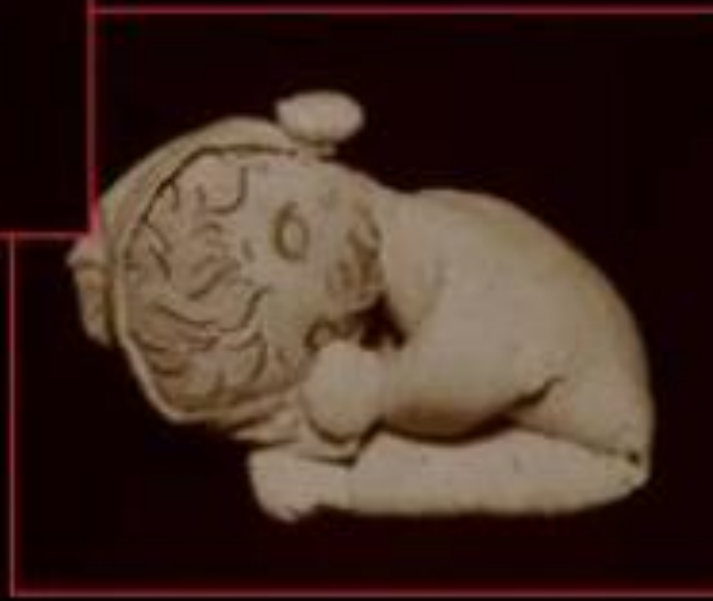
- • History of drug or teratogen exposure
- • Presence of polyhydramnios
- • Maternal diseases (diabetes, epilepsy)
- • Parental age
- • Consanguinity
- • Family history of neuromuscular disease
- • Other affected siblings

Neonatal Hypotonia

- **History**
  - History since delivery
    - Respiratory effort
    - Ability to feed
    - Level of alertness
    - Level of spontaneous activity
    - Character of cry
    - Apgar scores
    - Resuscitation requirements

Neonatal Hypotonia

- **History**
  - Any significant family history
    - Affected parents
    - Siblings
    - Consanguinity
    - Stillbirths
    - Childhood deaths

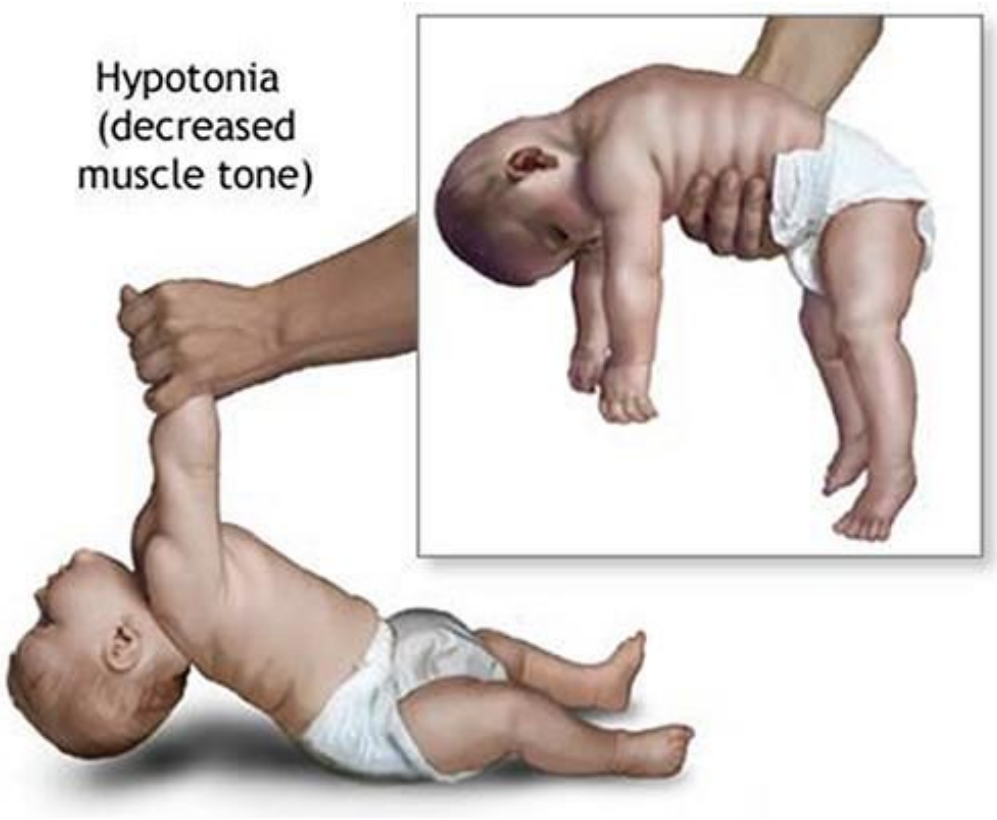


Rag doll

Hypotonia (decreased muscle tone)

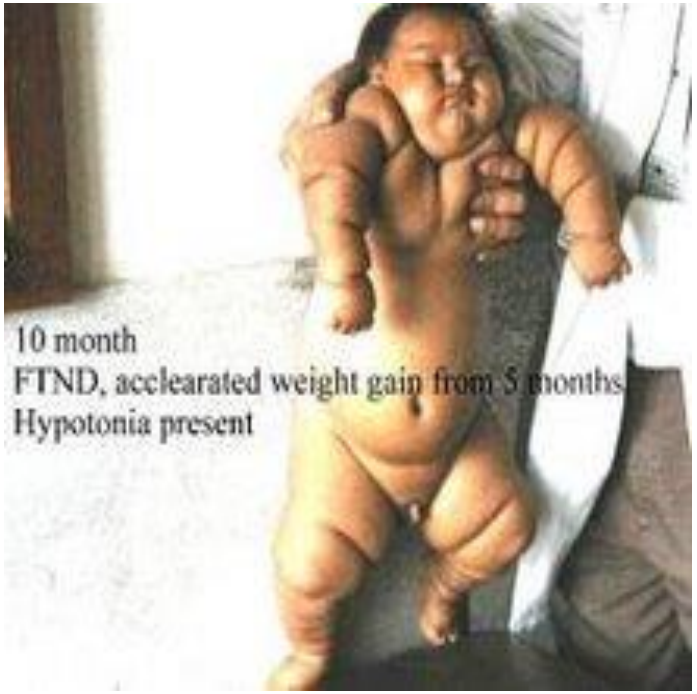
Neonatal Hypotonia

- Identification of hypotonia
  - Holding the infant in horizontal suspension
  - The back hangs over the examiner's hand, and the limbs and head hang loosely
  - Passive extension of the legs at the knees no resistance is met
  - Pulling the infant from the supine to sitting position the head lags and continues to lag when the sitting position is reached



Neonatal Hypotonia

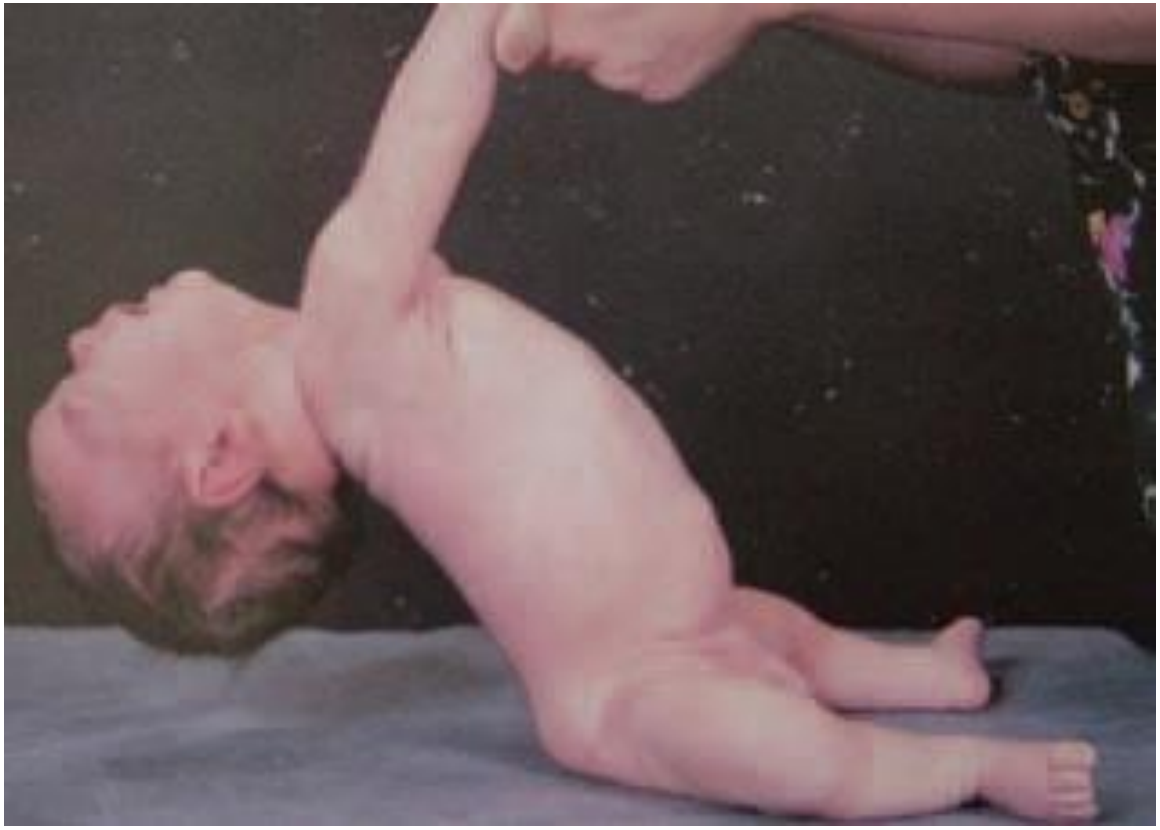
- Identification of hypotonia
  - Holding the infant under the arms
  - The legs will be extended
  - Decreased tone of the shoulder girdle allows the infant to slip through the examiner's hands



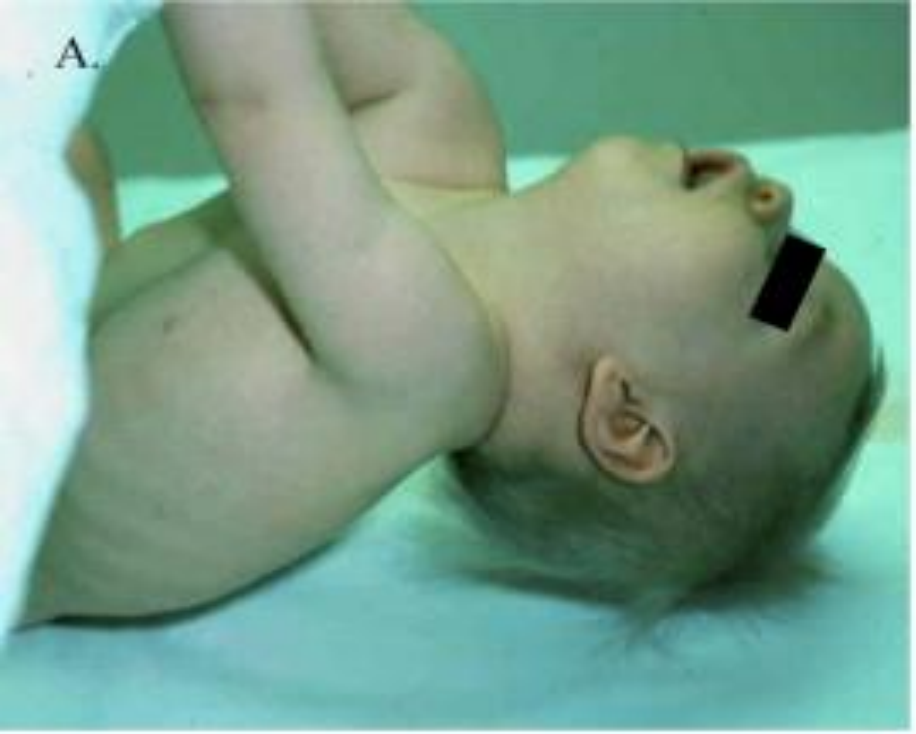
Scarf Sign

- Put the child in a supine position and hold one of the infant's hands.
- Try to put it around the neck as far as possible around the opposite shoulder.
- Observe how far the elbow goes across the body.
- In a floppy infant, the elbow easily crosses the midline.

The same infant in horizontal suspension. Note the inverted U posture.



*A 12-week-old male infant with excessive head-lag evident on '**pull-to-sit**'. Note the hypotonic posture of the legs with external rotation.*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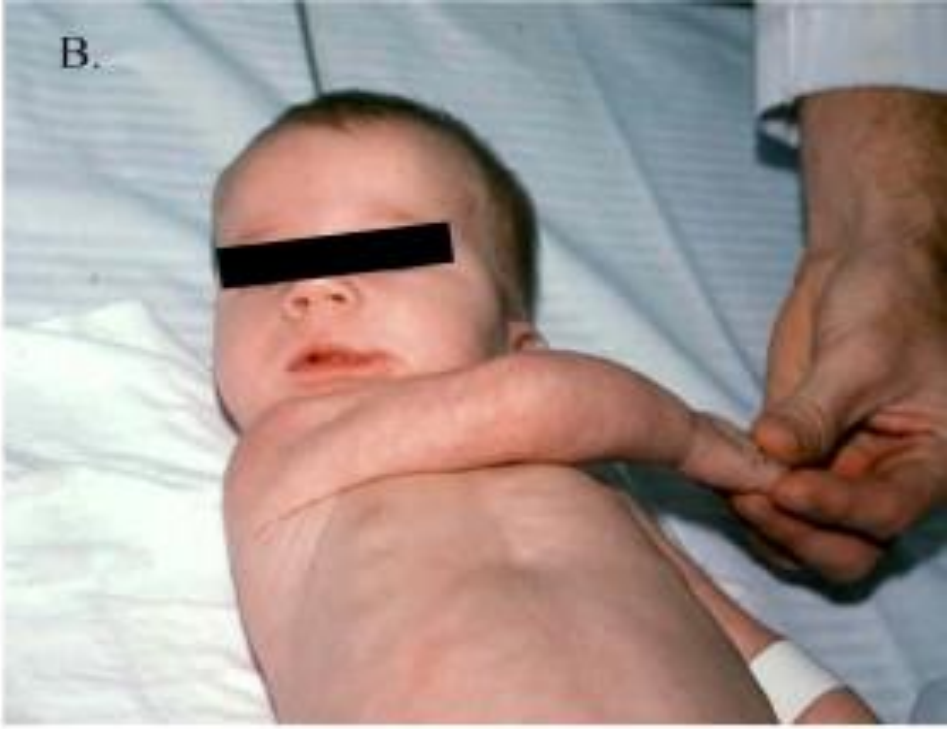
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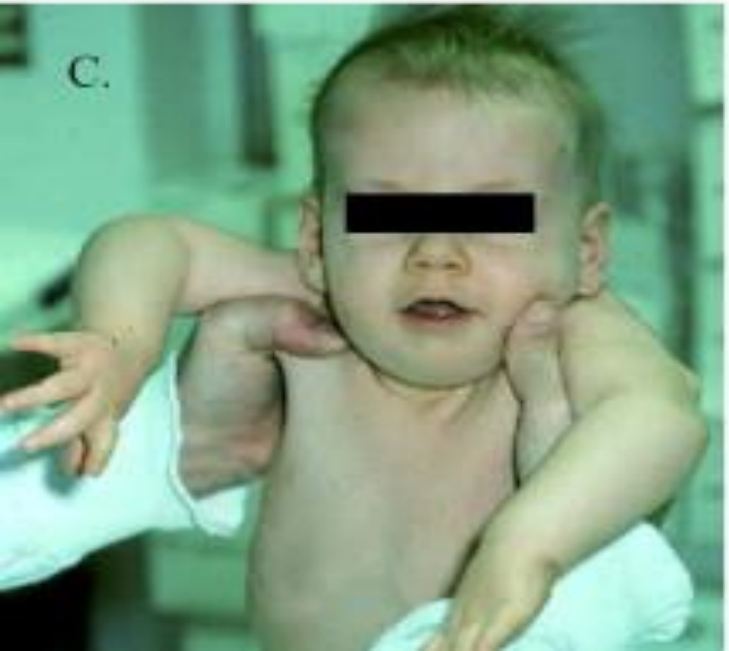
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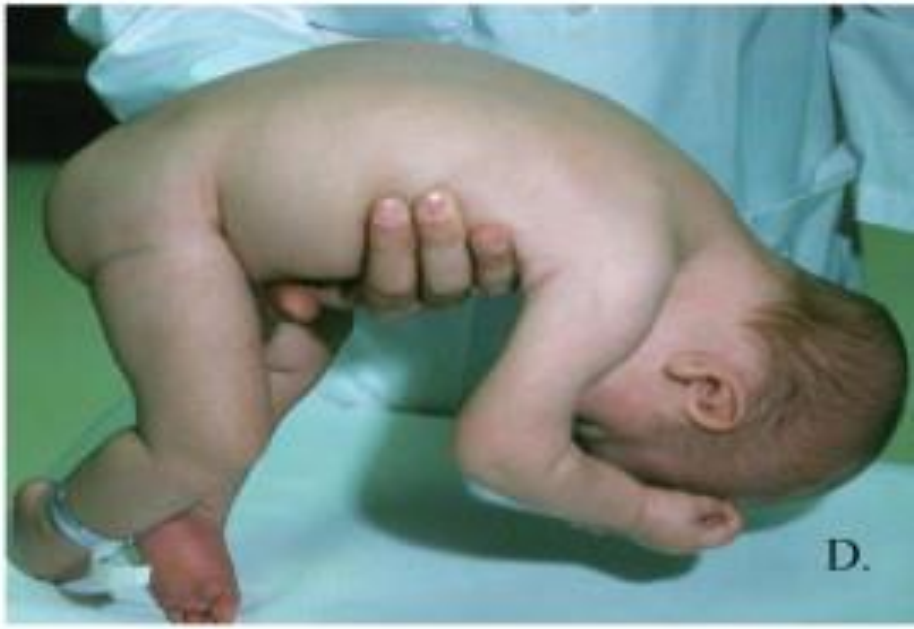
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The Floppy Infant Presenting Features

- Hypotonia
  - Abnormal postures
  - Diminished resistance to passive movement
  - Abnormal range of joint movement
- Delay in motor milestones

LOCALIZATION

LOCALIZATION

Classification(Location)

- Brain
- Spinal cord
- Peripheral nerves
- Neuromuscular Transmission
- Muscles
- Systemic disorders

Table 1 Localization in the Floppy Infant

Origin of Hypotonia	Structural Localization	Clinical Pathological Conditions
Supraspinal/suprasegmental hypotonia (preserved DTR)	Brain	Systemic illness (sepsis, CHF, HIE)
	Brainstem	Syndromic hypotonia
		Cerebral dysgenesis
		Grossly normal brain
	Craniovertebral junction	Spinal cord injury
Segmental or motor unit hypotonia (DTR depressed or lost)	Anterior horn cell	Spinal muscular atrophy
	Peripheral nerve	HMSN
	Neuromuscular junction	Myasthenia gravis, congenital myasthenic syndromes, botulism
	Muscle	Congenital myopathies, metabolic myopathies, neonatal presentation of muscular dystrophy

DTR = myotatic reflexes (deep tendon reflexes); CHF = congestive heart failure; HIE = hypoxic ischemic encephalopathy; HMSN = hereditary motor sensory neuropathy.

Bodensteiner JB. The evaluation of the hypotonic infant. Semin Pediatr Neurol. 2008

Neonatal Hypotonia

- **Physical Examination**
  - **Clues and Pitfalls**
    - Profound central hypotonia may have absent DTR
    - Absent DTR in the first few DOL would not rule out a central cause for the hypotonia

Neonatal Hypotonia

- **Physical Examination**
  - **Clues and Pitfalls**
    - Presence of profound weakness and hypotonia suggest:
      - Disorder of the lower motor neuron
        - A sign of this may be a weak cry
    - Weakness is uncommon in central hypotonia except in the acute stages

Neonatal Hypotonia

- **Physical Examination**
  - **Clues and Pitfalls**
    - Arthrogryposis (the fixation of joints at birth)
      - Associated with:
        - Neonatal hypotonia
        - More commonly with lower motor neuron unit
        - Multisystem abnormalities

Neonatal Hypotonia

Clues in cerebral hypotonia

Cerebral Hypotonia in newborns usually does not pose diagnostic difficulty. The history and physical examination identify the problem.

- Normal or Brisk reflexes
- Other abnormal brain functions: delay, seizures
- Fisting
- Movement through postural reflexes
- Scissoring on vertical suspension
- Dysmorphic features
- Extra-cranial organ malformations

Neonatal Hypotonia

Clues in motor unit hypotonia

Disorders of the motor unit are not associated with malformations of other organs except for joint deformities and the mal development of bone structures.

- Absent or Depressed reflexes
- Intact brain function
- Muscle atrophy
- Fasciculations
- Failure of movement through postural reflexes
- No extra-cranial organ malformations

Neonatal Hypotonia

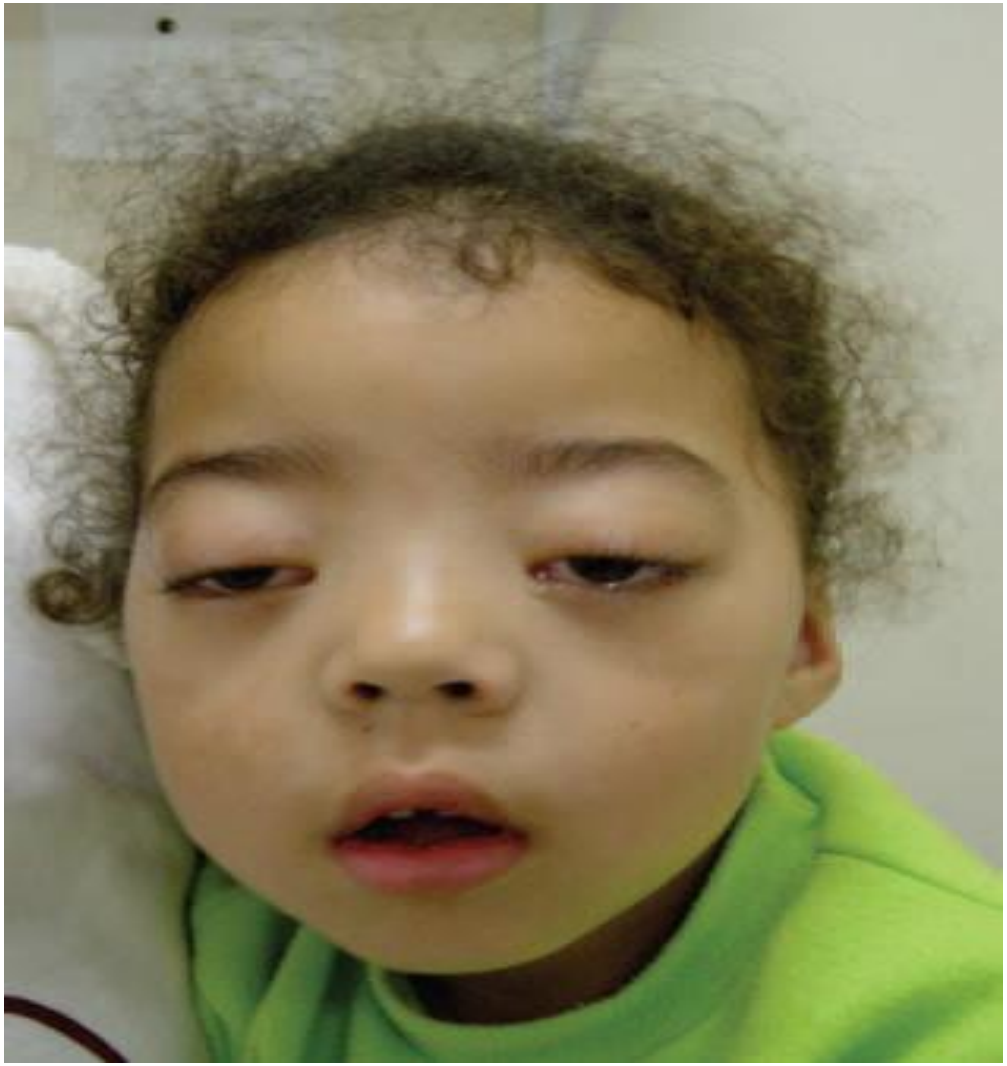
- **Physical Examination**
  - **Anterior horn cells**
    - Generalized weakness
    - Decreased/ absent DTRs
    - Fasciculations
    - Often described as alert

Neonatal Hypotonia

- **Physical Examination**
  - **Nerve**
    - Weakness, distal>proximal
    - Decreased/ Absent DTRs
    - +/- fasciculations

Neonatal Hypotonia

- **Physical Examination**
  - **Neuromuscular Junction**
    - Weakness, face/ eyes/ bulbar
    - Normal DTRs
    - No fasciculations



Ptosis and external ophthalmoplegia in a floppy weak child. Suggestive of myasthenia gravis.

Neonatal Hypotonia

- **Physical Examination**
  - **Muscles**
    - Weakness, proximal>distal
    - Decreased DTRs

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D.D. of Floppy Infant Syndrome

- **Physical Examination**
  - **Clues**
    - Abnormal odor
      - Metabolic disorders
    - Hypopigmentation, undesceded testes
      - Prader Willi
    - Hepatomegaly
    - Retinitis pigmentosa
      - Neonatal adrenoleukodystrophy

D.D. of Floppy Infant Syndrome

- **Physical Examination**
  - **Clues**
    - Abnormal odor
      - Metabolic disorders
    - Hypopigmentation, undesceded testes
      - Prader Willi
    - Hepatomegaly
    - Retinitis pigmentosa
      - Neonatal adrenoleukodystrophy

D.D. of Floppy Infant Syndrome

Central nervous system

- Perinatal asphyxia, neonatal, encephalopathy, kernicterus, cerebral palsy (atonic type).
- Intracranial hemorrhage.
- Cerebral malformations
- Chromosomal abnormalities (e.g.Trisomy 21, Prader-Willi syndrome)
- Congenital infection TORCH
- Acquired infections
- Peroxisomal disorders
- Drug effects (e.g. benzodiazepines)
- Inborn errors of metabolism e.g., aminocidurias, mucopolysaccharidosis and cerebral lipidosis.

Hypotonic cerebral palsy

- Many hypotonic children due to causes in central nervous system are mentally retarded.
- In atonic or hypotonic cerebral palsy, reflexes are brisk in spite of generalized flaccidity.
- Floppy infant due to cerebral causes is associated with lethargy, poor feeding, and lack of alertness, poor Moro's reflex, and seizures during the neonatal period.

D.D. of Floppy Infant Syndrome

Spinal cord

- Spinal Cord Injury – Broken Neck
- Infections
  - Enterovirus - POLIO
  - Transverse Myelitis
- Mass lesions

D.D. of Floppy Infant Syndrome

Injuries in Breech Presentation

- Injuries to the cervical spinal cord occur almost exclusively during vaginal delivery;
- approximately 75% are associated with breech presentation and 25% with cephalic presentation.
- Because the injuries are always associated with a difficult and prolonged delivery, decreased consciousness is common, and hypotonia is falsely attributed to asphyxia or cerebral trauma.

- MRI of the spine shows intraspinal edema and hemorrhage

D.D. of Floppy Infant Syndrome

Injuries in Cephalic Presentation

- Twisting of the neck during midforceps rotation causes high cervical cord injuries in cephalic presentation.
- The trunk fails to rotate with the head.
- The risk is greatest when amniotic fluid is absent because of delay from the time of membrane rupture to the application of forceps.

D.D. of Floppy Infant Syndrome

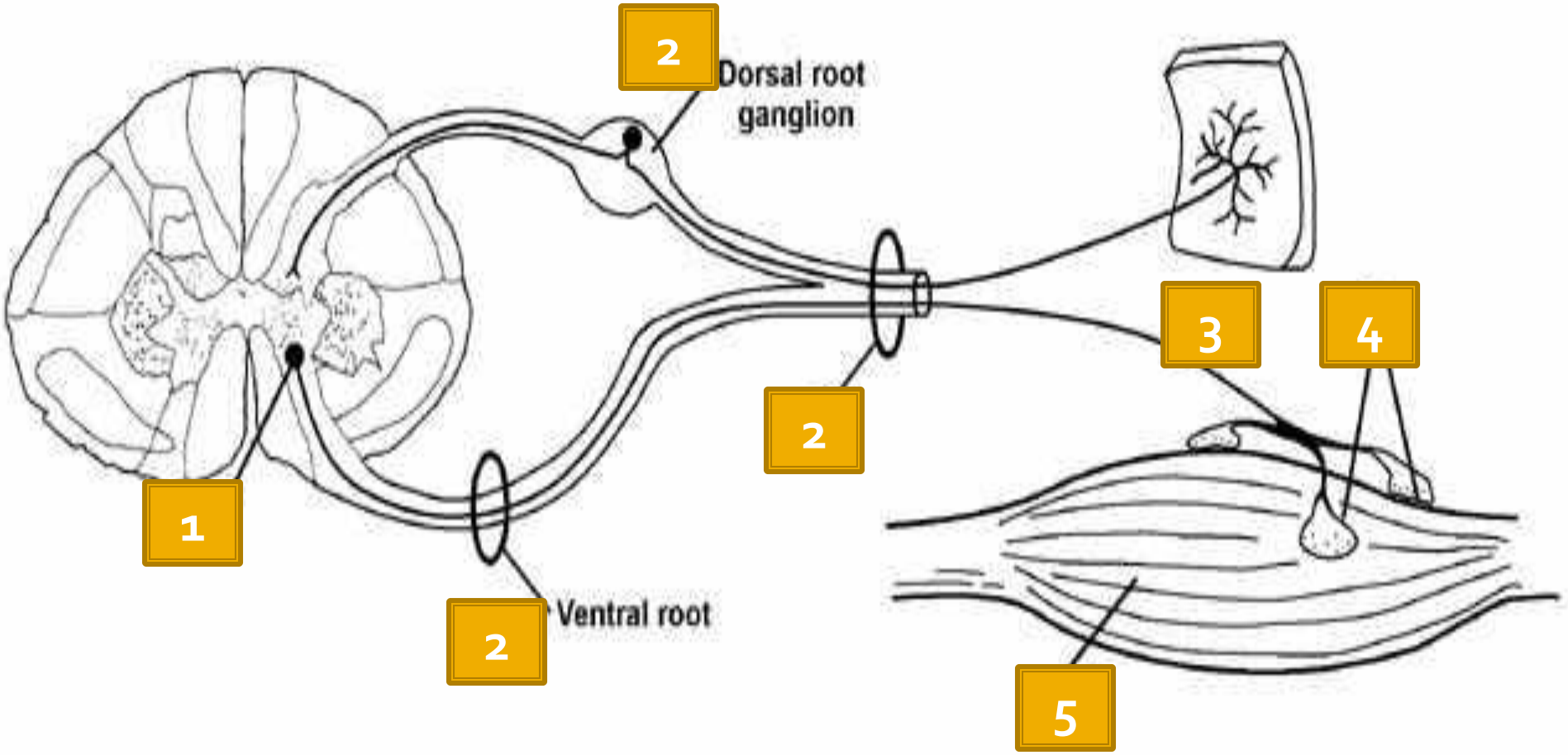
Poliovirus Infection

- Small RNA virus : Neurotropic
- Seasonal epidemics
- Prodromal illness
- Pain --> Asymmetric Paralysis
- Rare but still occurs
- vaccine related : 1 in 12 million

D.D. of Floppy Infant Syndrome

Mass lesions of spinal cord

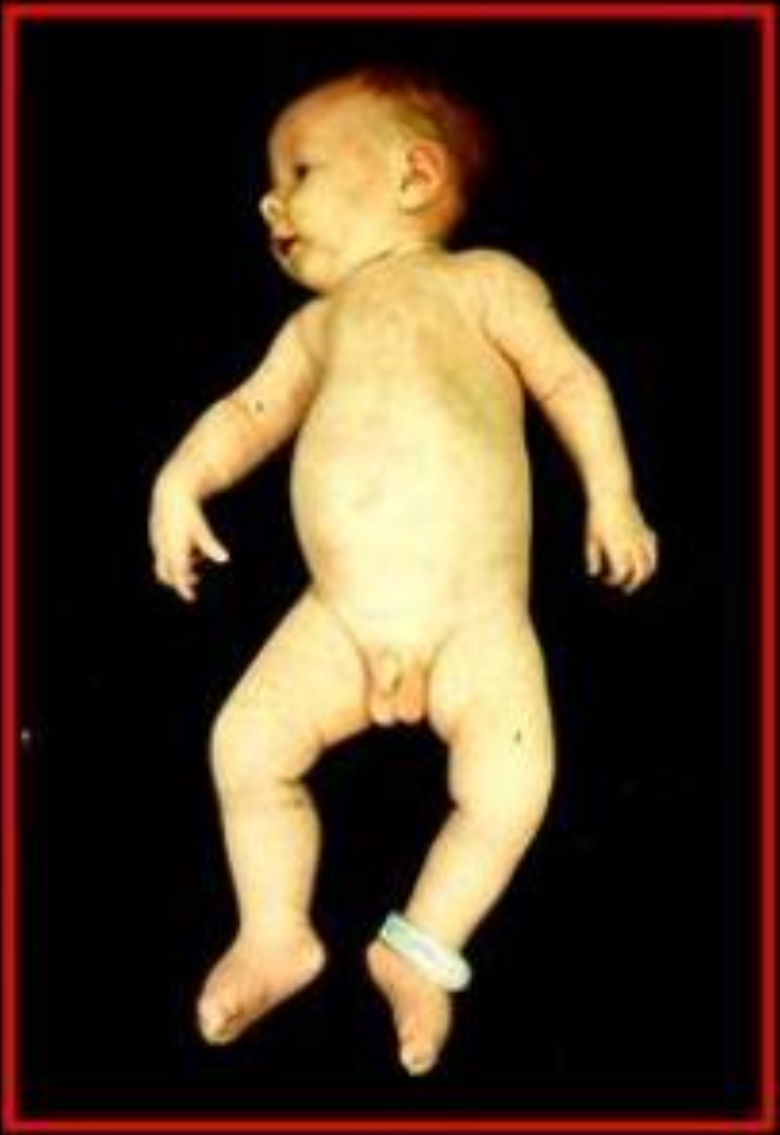
- Rare
- Intra-Abdominal Tumors
- Neuroblastoma
- Early in Infancy



1. The anterior (ventral) horn cell
2. The radicle (root).
3. The peripheral nerve.
4. The neuromuscular junction.
5. The muscle.

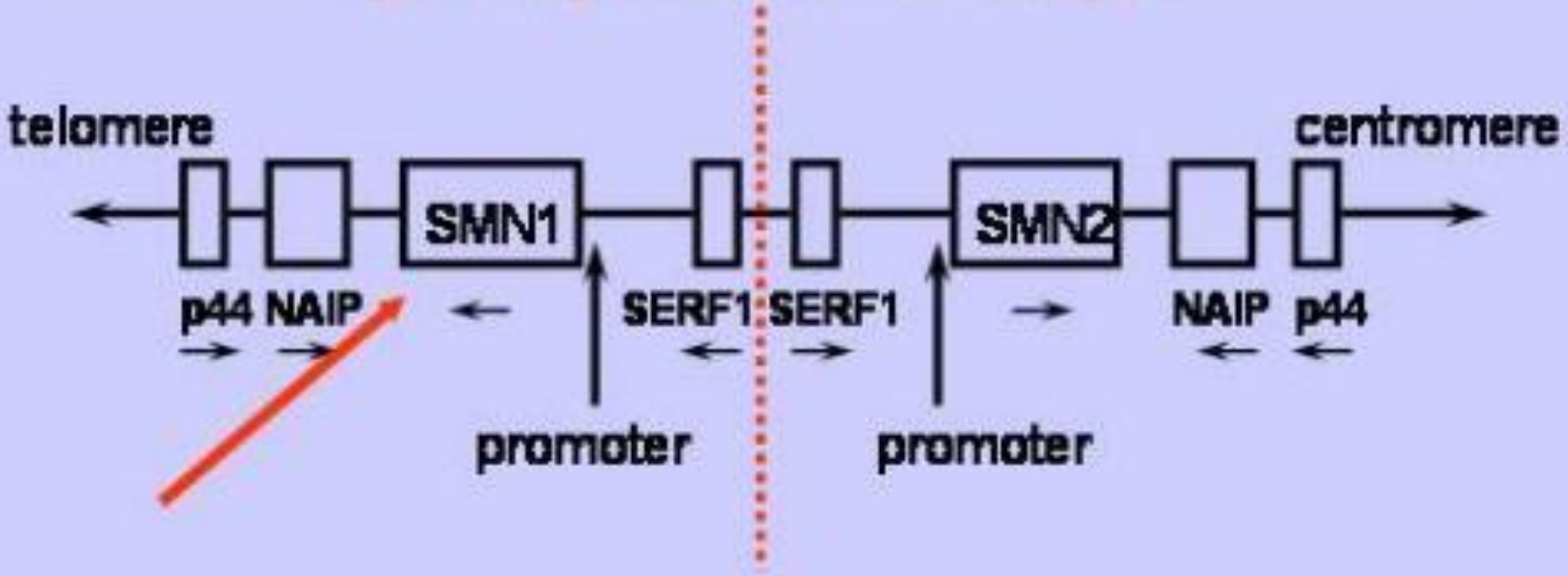
Werdning-Hoffman Syndrome
SMA type 1

- Anterior Horn cell (neuronal) degeneration
- Progressive Weakness: Proximal > Distal
- Hypotonia
- Areflexia
- Atrophy / Fasciculations
- Intact Brain Development



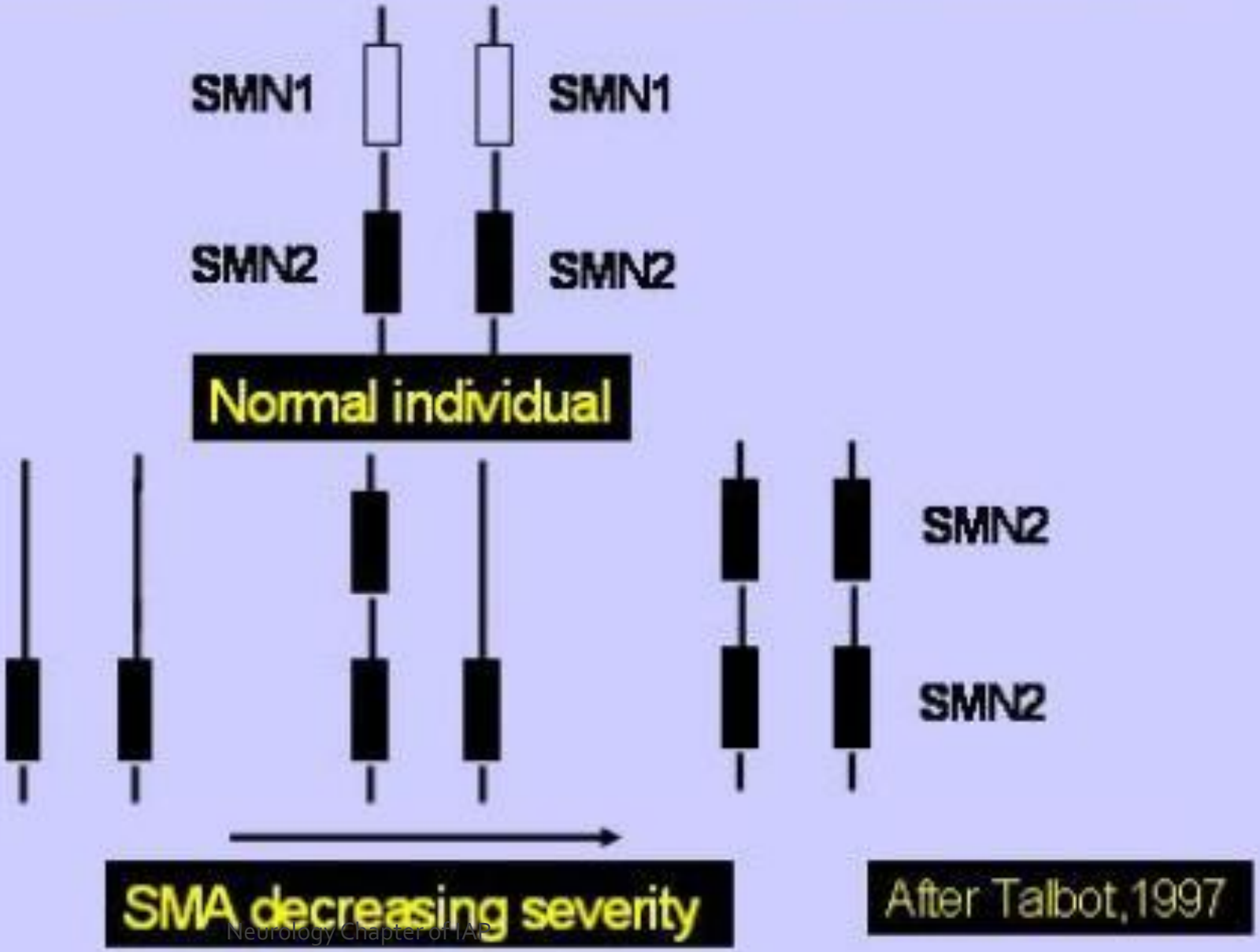
Severe SMA: Werdnig-Hoffmann disease

The Survival of Motor Neurones (SMN) Locus on 5q13



* Total deletion of SMN2 not pathogenic
* Total deletion of SMN1 causes SMA
* Total deletion of SMN1 and SMN2 is lethal before implantation

Chromosome combinations



Diaphragmatic SMA

SMA

Diaphragmatic SMA

- Paradoxical diaphragmatic movements
- Antigravity movements in the 4 limbs
- Finger contractures; sometimes talipes
- Difficulties with feeding
- Low pitch cry
- **Mutations in the IGHMBP2 gene**
  (immunoglobulin μ-binding protein 2)
  on chromosome 11q

SMA

- SMA is the second most common autosomal recessive disease in the US after cystic fibrosis.
- Incidence:
  - Type 1: 1 per 10,000 live births
  - Types II and III: 1 per 24,000 births

- Worldwide 7.8-10 cases per 100,000 live births
- ? M:F predominance or M>F
- No ethnic predominance.

SMA

- The genetic defects associated with SMA types I-III are localized on chromosome 5q11.2-13.3.
- Mutations in the *SMN* gene result in a loss of function of the SMN protein.
- Many classification systems based on inheritance, clinical, and genetic criteria.

SMN Gene Testing

- Reliable and unequivocal diagnostic confirmation in 98.5% of cases
- Subtle gene abnormalities in the remaining cases with typical clinical features
- No simple correlation between disease severity and result of the gene test
- Clinical involvement of bulbar and chest muscles determines survival, not age at onset

SMA Type 1

- *SMA type I*, (Werdnig-Hoffmann acute infantile), occur birth – 6 months (95% by 3 months)
- Severe, progressive muscle weakness and flaccid or reduced muscle tone (hypotonia).
- Bulbar dysfunction includes poor suck ability, reduced swallowing, and respiratory failure.
- Patients have no involvement of the extraocular muscles, and facial weakness is often minimal or absent.
- They have no evidence of cerebral involvement, and infants appear alert.

SMA Type 1

- Impaired fetal movements are observed in 30% of cases
- 60% of infants with SMA type I are floppy babies at birth. Prolonged cyanosis may be noted at delivery.
- In some instances, the disease can cause fulminant weakness in the first few days of life. Such severe weakness and early bulbar dysfunction -> mean survival of 5.9 months.
- Affected children never sit or stand.
- In 95% of cases, infants die from complications of the disease by 18 months.

SMA Type 2

- *SMA type II* (chronic infantile, sitters) usually begin between 6 - 18 months.
- Most common form of SMA
- Most common manifestation is developmental motor delay. Infants with SMA type II often have difficulties with sitting independently or failure to stand by 1 year of age.
- These children may learn to sit but will never be able to stand or walk.

SMA Type 2

- An unusual feature of the disease is a postural tremor affecting the fingers. This is thought to be related to fasciculations in the skeletal muscles
- Pseudohypertrophy of the gastrocnemius muscle, musculoskeletal deformities, and respiratory failure can occur.
- The lifespan of patients with SMA type II varies from 2 years to the third decade of life. Respiratory infections account for most deaths.

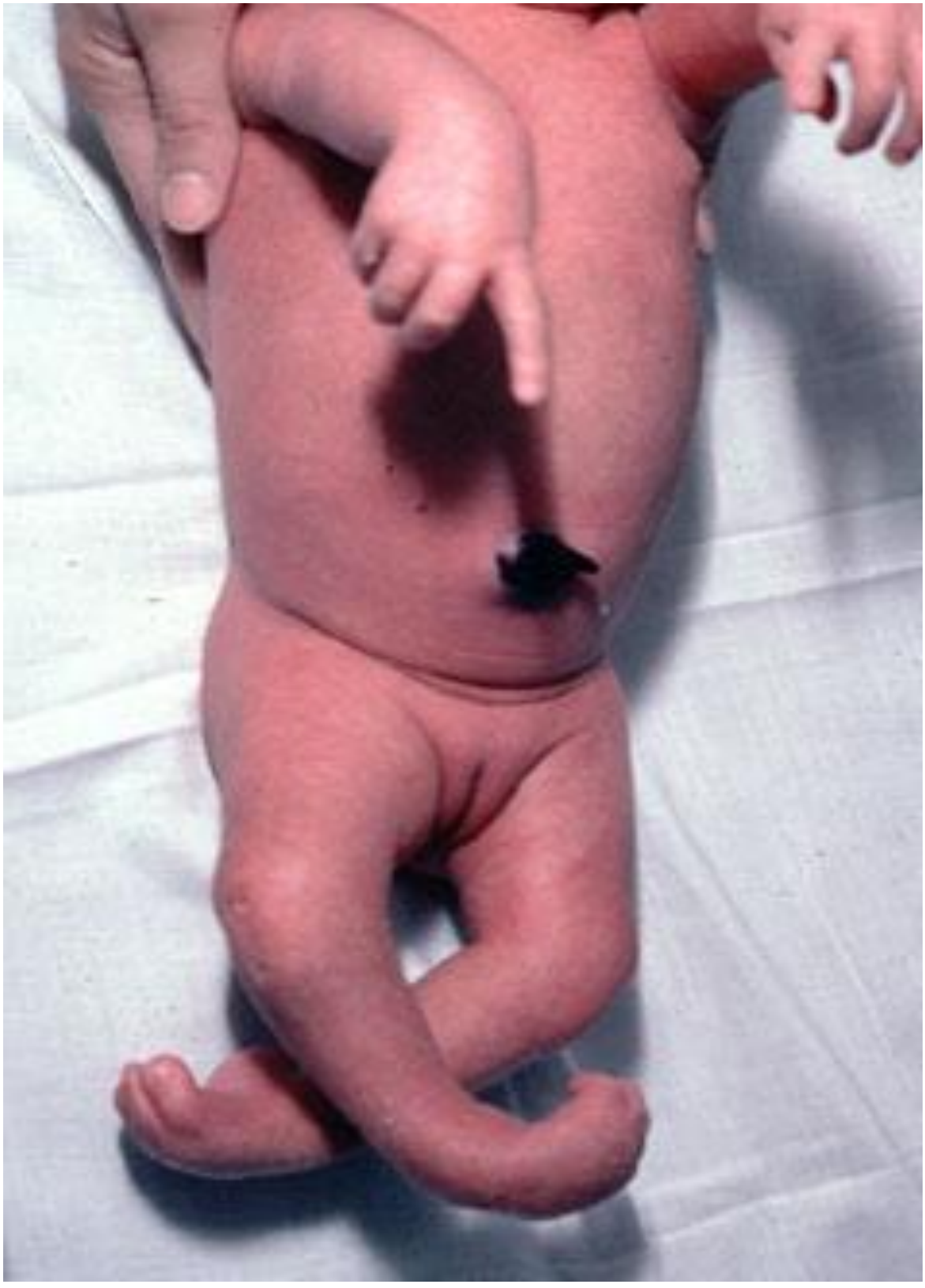
SMA Type 3

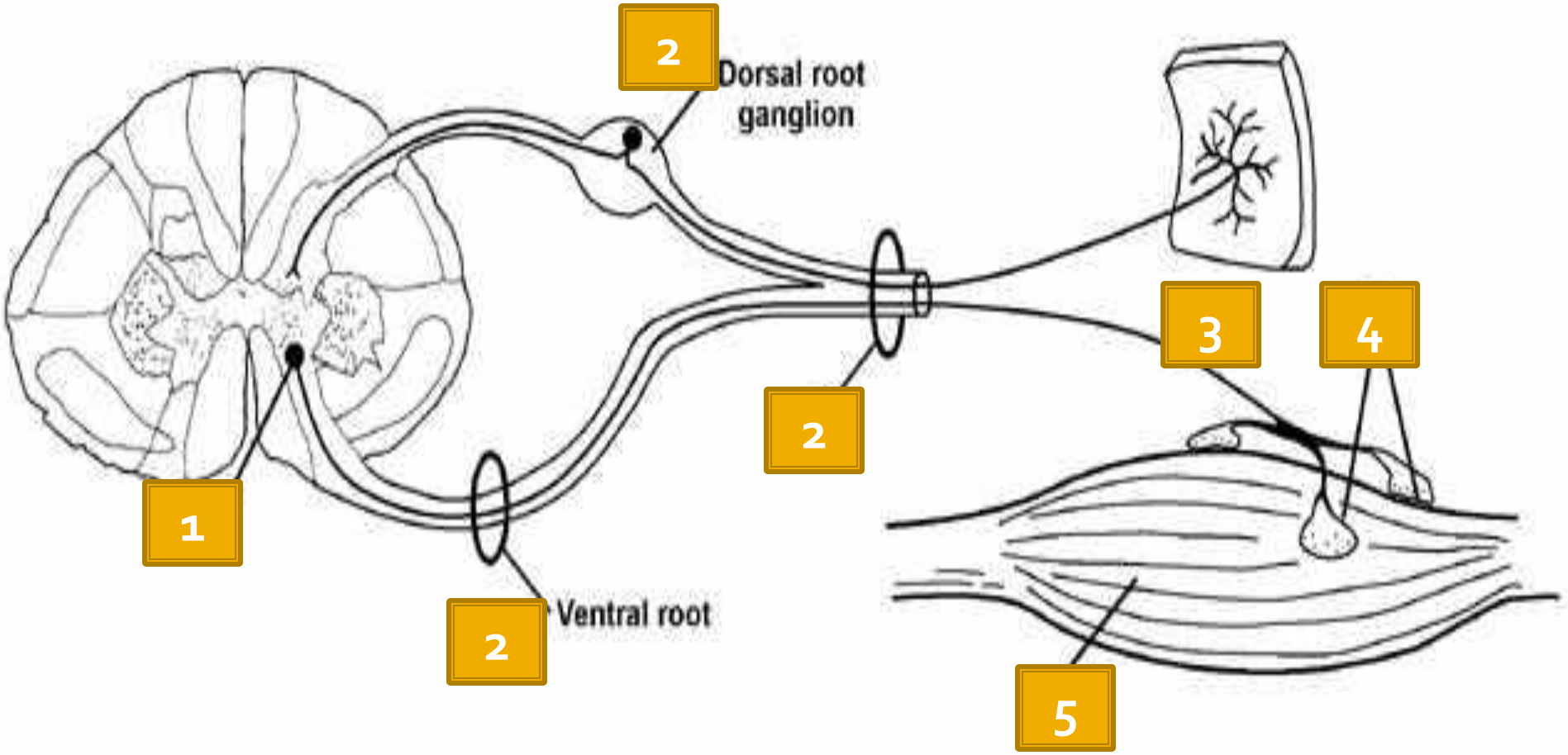
- *SMA type III (Kugelberg-Welander,* chronic juvenile, walkers*)* appear 18 months – adult.
- Slowly progressive proximal weakness. Most can stand and walk but have trouble with motor skills, such as going up and down stairs.
- Bulbar dysfunction occurs late in the disease.
- Patients may show evidence of pseudohypertrophy.
- The disease progresses slowly, and the overall course is mild. Many patients have normal life expectancies.

SMA

- *Congenital SMA with arthrogryposis* (persistent contracture of joints with fixed abnormal posture of the limb) is a rare disorder. Manifestations include

1. severe contractures,
2. curvature of the spine,
3. chest deformity,
4. respiratory problems,
5. an unusually small jaw, and
6. drooping upper eyelids.





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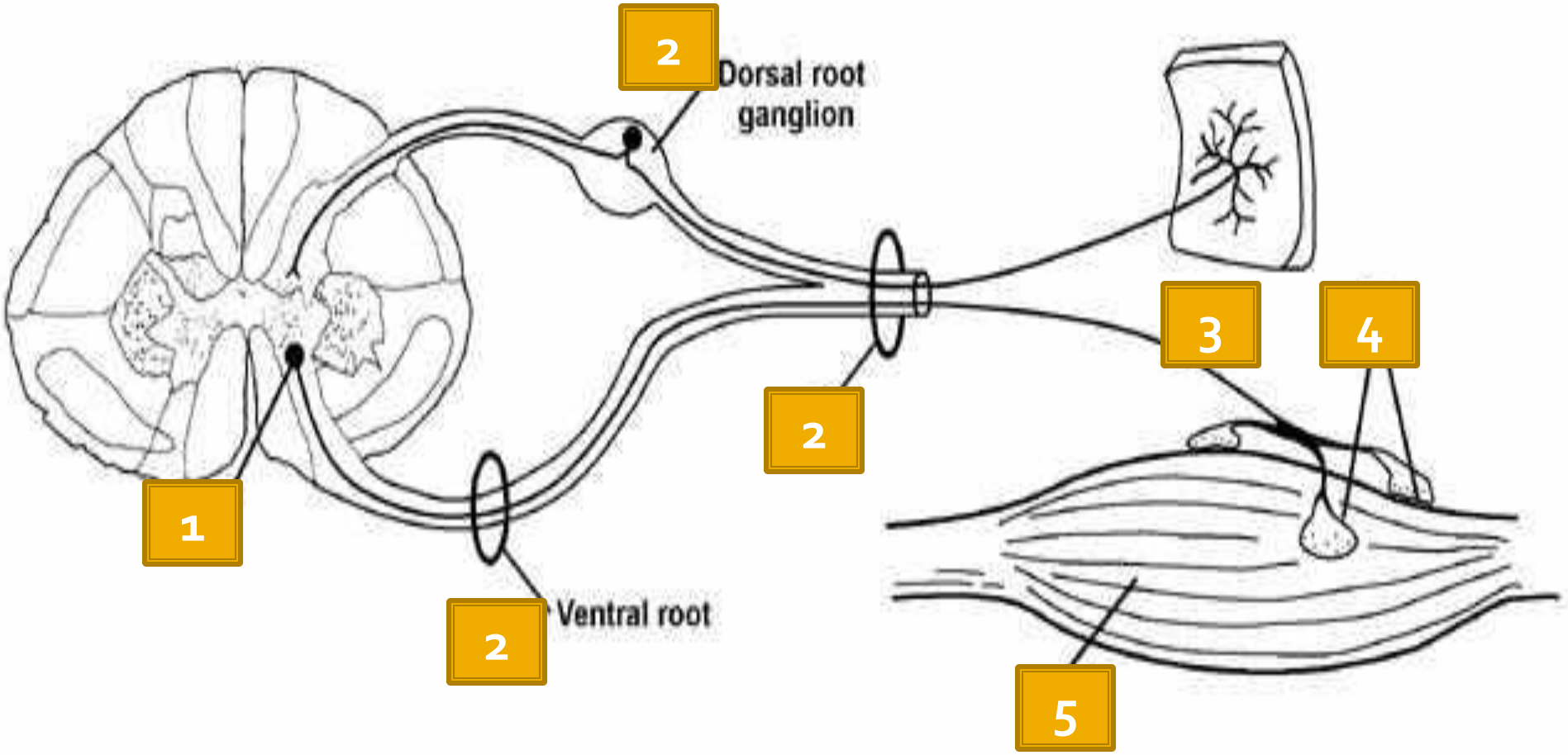
2. The radicle (root).
3. The peripheral nerve.
4. The neuromuscular junction.
5. The muscle.

Peripheral Nerves

- Polyneuropathy
- Dysmyelination
  - Autoimmune
  - Congenital / genetic
- Dysautonomia

Peripheral Nerves

- **Peripheral nerves**
  - Hereditary sensory motor neuropathies
    - Charcot-Marie-Tooth disease



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Neuromuscular junction

- Toxins
  - Botulism
- Myasthenia
  - Congenital
  - Neonatal transitory

Infantile myasthenia

- FAMILIAL-INFANTILE
  - Multiple Genetic Defects: AR + AD
  - Pre & Post Synaptic AChR abnormalities
  - Respiratory or feeding problems at birth
- CONGENITAL
  - Usually Bilateral Ptosis & Ophthalmoplegia
  - Multiple Genetic Defects: AR
- NEONATAL-TRANSITORY
  - 10 - 15% of myasthenic mothers

Infantile myasthenia

Table 6 Selected Congenital Myasthenic Syndromes

Type of CMS	Clinical Features	Gene Defects
AchR deficiency	Early onset Variable severity Ptosis, extraocular palsy Bulbar, arm, and legs involved	AchR subunit genes *CHRNE* *CHRNA1* *CHRNB1* *CHRND* *SCN4A*
Slow-channel syndrome (SCCMS)	Selective severe weakness of neck, wrist, finger extensor Onset variable Severity variable Ventilatory problems common and may be progressive	
Fast-channel syndrome	Variable onset and severity May respond to AchE inhibitors	
Endplate rapsyn deficiency (EP rapsyn deficiency)	Early onset with hypotonia, respiratory failure, apnea, arthrogryposis Mild or severe involvement	*RAPSN*
CMS with episodic apnea (CMSEA)	Respiratory failure early Episodic apnea Improvement with age May respond to AchE inhibitors	*CHAT*
Endplate acetylcholineesterase deficiency (EP AchE deficiency)	Severe Ophthalmoparesis Severe axial musculature weakness Slow pupillary responses	*COLQ* C-terminal missense mutations may be milder

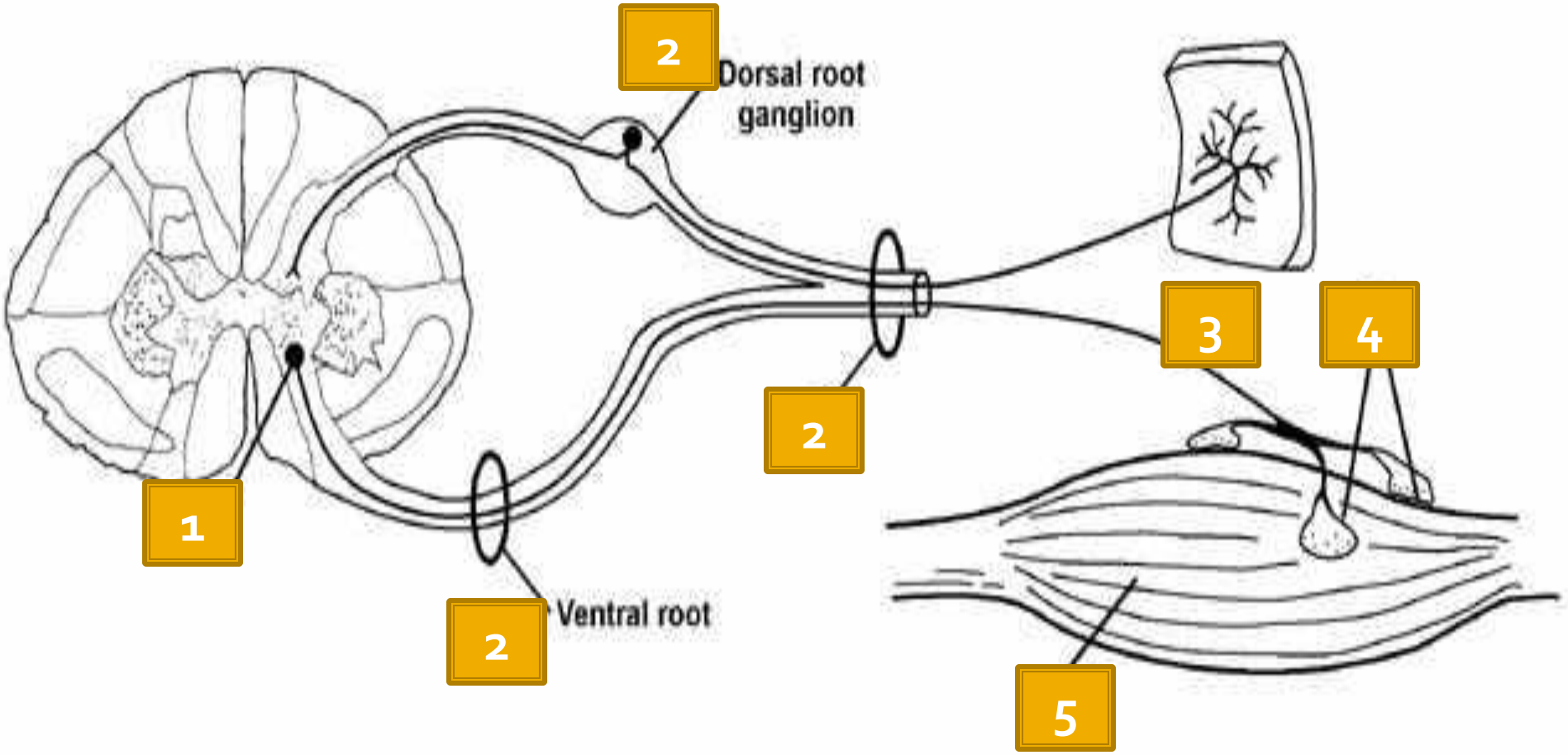
The CHRN genes code for different subunits of the AchR. COLQ codes for the collagenic tail subunit of the acetylcholinesterase. CHAT is the gene for choline acetyltransferase, RAPSN codes for rapsyn, and the SCN4A gene encodes the sodium channel in skeletal muscle.

Infantile botulism

- Infants usually 2 - 26 weeks old
- Clostridium Botulinum --> Exotoxin
- Prevents release of Acetylcholine
- Cholinergic Blockade of skeletal muscle
- Source of intestinal colonization usually unclear
- Occurs mainly between March & October

Infantile botulism

- Prodrome: poor feeding & constipation
- Progressive bulbar & general weakness
- Loss of deep tendon reflexes
- Hypotonia
- Dysphagia
- Ptosis
- Sluggish dilated pupils



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D.D. of Floppy Infant Syndrome

- **Muscle**
  - Muscular dystrophies (congenital myotonic dystrophy)
  - Congenital myopathies (e.g. central core disease)

D.D. of Floppy Infant Syndrome

- **Metabolic myopathies**
  - Acid maltase deficiency
  - Carnitine deficiency
  - Cytochrome-*c*-oxidase deficiency

D.D. of Floppy Infant Syndrome

Table 7 The Classical Congenital Myopathies

	Central Core Disease	Nemaline Myopathy	Centronuclear (myotubular) Myopathy
Presentation/Severity			
Infantile	Severe	Severe	Severe
Childhood	Moderate	Moderate	Moderate
Adult	Mild	Mild	Mild
Muscle wasting	No	Yes	Yes
Somatic abnormalities	Yes	Yes (infantile)	Yes (dominant)
Ocular muscle weakness	No	Yes	Yes with ptosis
Pain/cramps	No	Yes (adult onset)	No
Malignant hyperthermia	Yes (characteristic)	No	No
Cardiomyopathy	Occasionally	Rare	No
Mental retardation	No	No	No
Genetic defect(s)	Dominant: 19q13.1 (*RYR1* gene) Ryanodine receptor, Dihydropyridine-sensitive L-type Ca channel gene.	Dominant: 1q42, 1q22-q23 *TPM3* (tropomyosin-3 gene), *ACTA-1* gene	Dominant: 11q22
	?beta myosin heavy chain (cardiomyopathy)	Recessive: *NEB*(Nebulin)gene, ACTA-1 gene	Xlinked: *MTM1* (myotubularin gene)

Bodensteiner JB. The evaluation of the hypotonic infant. Semin Pediatr Neurol. 2008

D.D. of Floppy Infant Syndrome

Table 9 The Nonsyndromic Congenital Muscular Dystrophies

Disease	Gene/Protein/Testing	Clinical Features
Merosin-deficient CMD (MDC1A)	*LAMA2*/Alpha-2 Laminin/+	Severe, hypotonia, global weakness, Contractures, Scoliosis, MRI = abn white Matter signal, Do not walk, NL IQ
CMD with partial merosin deficiency (MDC1B)	*LAMA2*/Alpha-2 Laminin/- research only	Milder S Sx, most do walk, NL IQ, MRI normal, cardiomyopathy, contracture of elbow, knees, fingers
CMD type 1C (MDC1C)	*FKRP*/fukutin-related protein/+	Severe weakness, global involvement Contractures of elbows, knee, finger MRI normal, NL IQ, cardiomyopathy
CMD with ITGA7 mutations	*ITGA7*/Integrin alpha-7/-	Proximal weakness, torticollis, congenital hip dislocation
CMD with spine rigidity (CMD RSS)	*SEPN1*/Selenoprotein N/+	Rigid spine, elbow, hip, and ankle Sleep hypoventilation, progressive
Ullrich CMD	*COL6A1&2*/Alpha 1 & 2 Collagen VI or COL7A3/Alpha 3 collagen VI	Global weakness with contractures, Distal hyperextensibility, calf atrophy, NL IQ

CMD = congenital muscular dystrophy; NL IQ = normal intelligence; abn = abnormal.

Bodensteiner JB. The evaluation of the hypotonic infant. Semin Pediatr Neurol. 2008

D.D. of Floppy Infant Syndrome

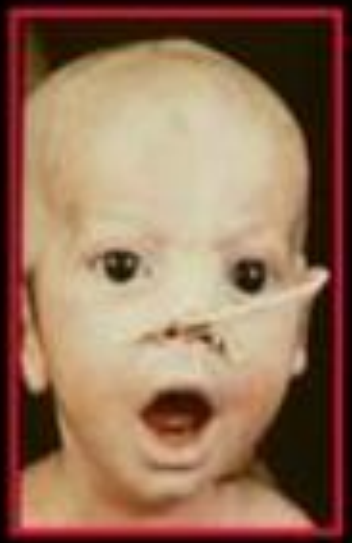
Table 10 Syndromic Congenital Muscular Dystrophies (Those With Brain Involvement)

Disease	Gene/Protein/Testing	Clinical Features
Fukuyama CMD (FCMD)	*FCMD*/fukutin/+	Generalized weakness (severe), Contractures, Cobblestone Lissencephaly
Muscle eye brain disease (MEB)	*POMGNT1*/protein -O-Mannoside beta-1,2-N-Acetylglucosaminyltransferase/+	Eye malformations without cataracts, Hydrocephalus, white-matter abn Cobblestone lissencephaly, milder as some walk but lose walking by age 20
Walker-Warburg syndrome	*POMT1*/protein-O-mannosyl-transferase −1-/+	Severe generalized weakness, Contractures at elbows only, lissencephaly, Dandy-Walker or cerebellar hypoplasia, flat pons, early demise
Walker-Warburg syndrome 2	*POMT2*/protein-O-mannosyl-transferase −2/+	Clinically indistinguishable from W-W-1
Congenital muscular dystrophy 1D (CMDC1D)	*LARGE*/glycosyltransferase-like protein (LARGE)/+	Global delay, muscle hypertrophy, Facial sparing, MRI changes in white matter, proximal > distal weakness

Bodensteiner JB. The evaluation of the hypotonic infant. Semin Pediatr Neurol. 2008

Congenital muscular dystrophy (CMD)

2 w.



9m. Floppy infant
Not weak
Normal development
Lax ligaments

Systemic

Genetic disorders

- Prader-willi
- Angelman's syndrome
- Cri du chat
- Cerebro-hepato-renal sydrome
- William's syndrome
- Trisomy 21
- Trisomy 13

Systemic

Metabolic

- Mitochondrial
- Congenital lactic acidosis
- Hyperammonemia
- Aminoacidurias
  - Non-ketotic hyperglycinemia
- Celiac disease

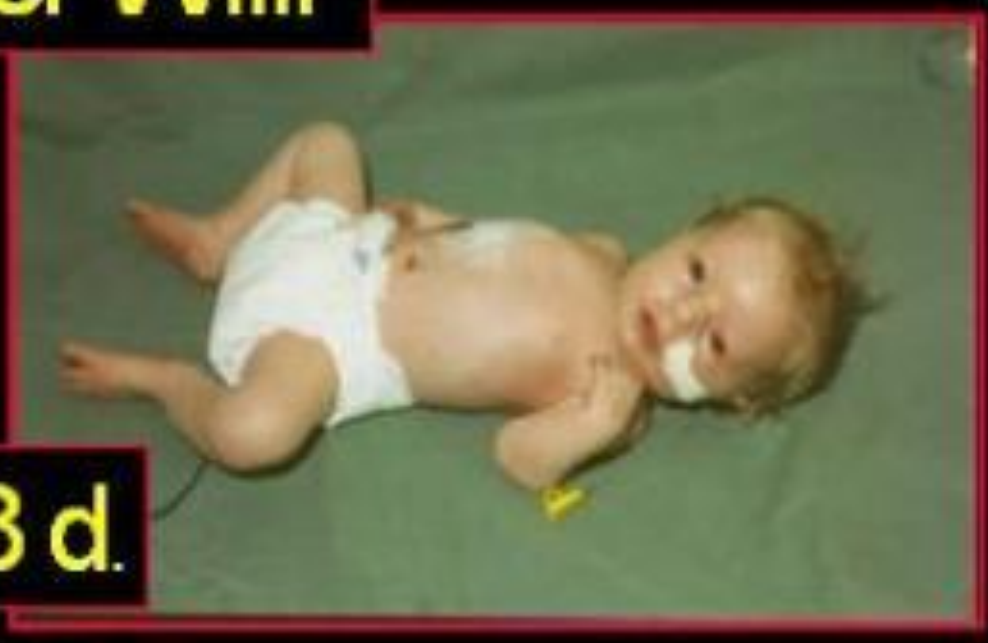
Prader Willi Syndrome
Cardinal features

- Profound hypotonia
- Swallowing difficulty
- No respiratory distress
- Low birthweight
- Characteristic facies ; fair hair
- Antigravity movement of limbs

Prader Willi Syndrome

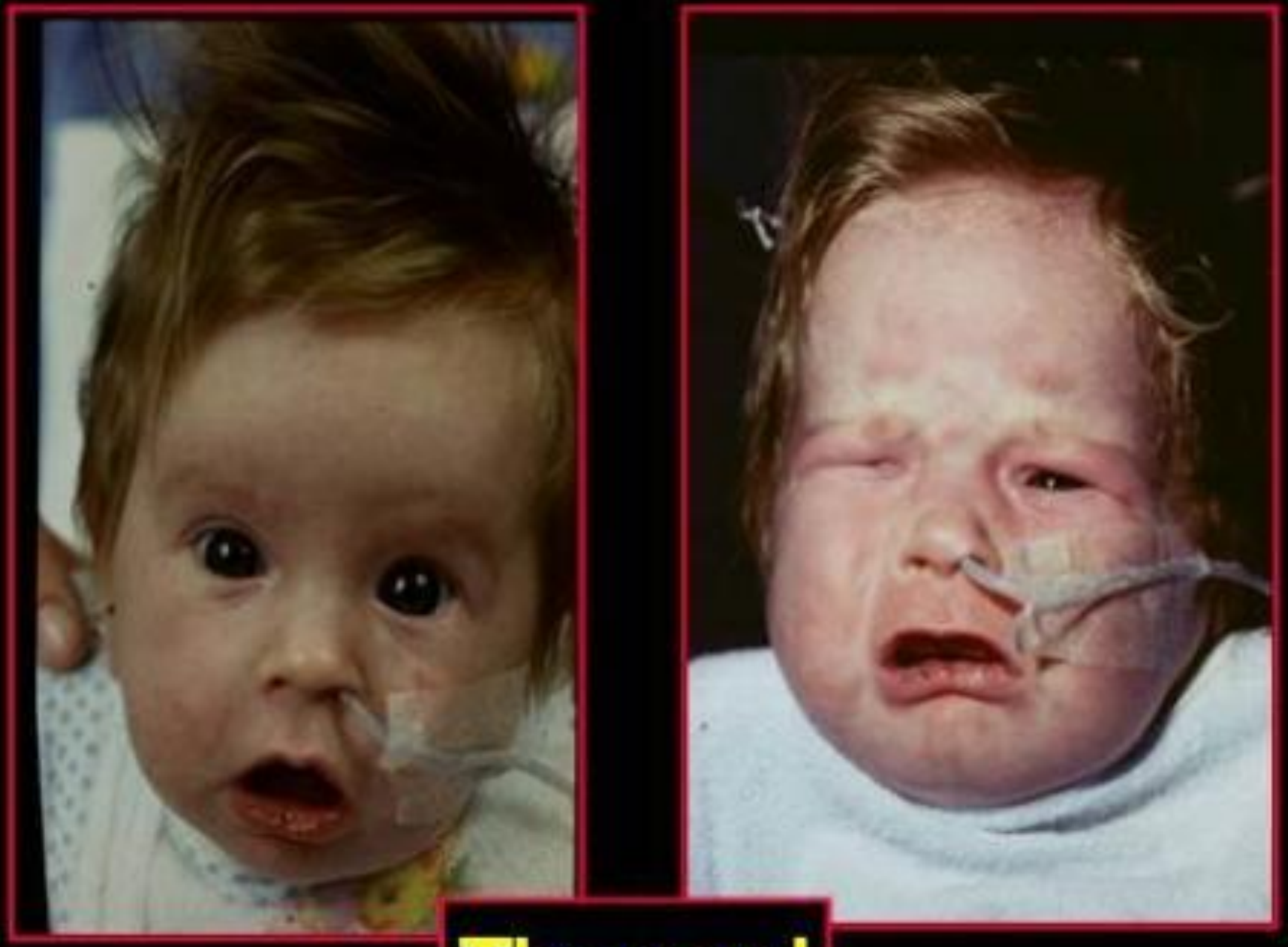
- Deletion chromosome 15q
- Imprinting
- Paternal chromosome
- Submicroscopic molecular deletions
- *Snprn* protein

Prader Willi



18 d.

2 m.



Prader-Willi syndrome

- Hypogenitalism 100%
- Cryptorchidism 84%
- Decreased Fetal Movement 75%
- Congenital Hip Dislocation 10%
- Clubfoot 6%
- Profound Infantile Hypotonia
- Mental Retardation
- Decreased / Absent DTRs
- Short Stature
- Obesity / Insatiable Appetite

Investigations

- **Investigation**
  - Central Causes
    - Neuroimaging
      - Ultrasound scan in the first instance
      - MRI for structural abnormality
      - EEG: if seizures suspected

Investigations

- **Investigation**
  - Central Causes
    - Genetics review if any dysmorphic features present
    - Karyotype (if dysmorphic features)
    - TORCH screen
    - DNA methylation studies or FISH for Prader-Willi syndrome (if clinically indicated after a genetics review)
    - Metabolic work up

Investigations

Metabolic evaluation

- Arterial Blood: Lactate, Pyruvate, ABG
- Venous Blood: Ammonia, Chemistries CBC, Carnitine profile, Amino Acids
- Urine: Organic & Amino Acids
- CSF: Lactate, Amino Acids (Glycine)
- Muscle: It Depends

Investigations

- **Investigation**
  - **Peripheral causes**
    - Creatine kinase: If elevated in an early sample, repeat after a few days.
    - Nerve conduction studies
    - Muscle biopsy
      - Depending on clinical situation, may be delayed until around 6 months of age as neonatal results are difficult to interpret

Investigations

- **Investigation**
  - **Peripheral causes**
    - Molecular genetics – CTG repeats, deletions in SMN gene

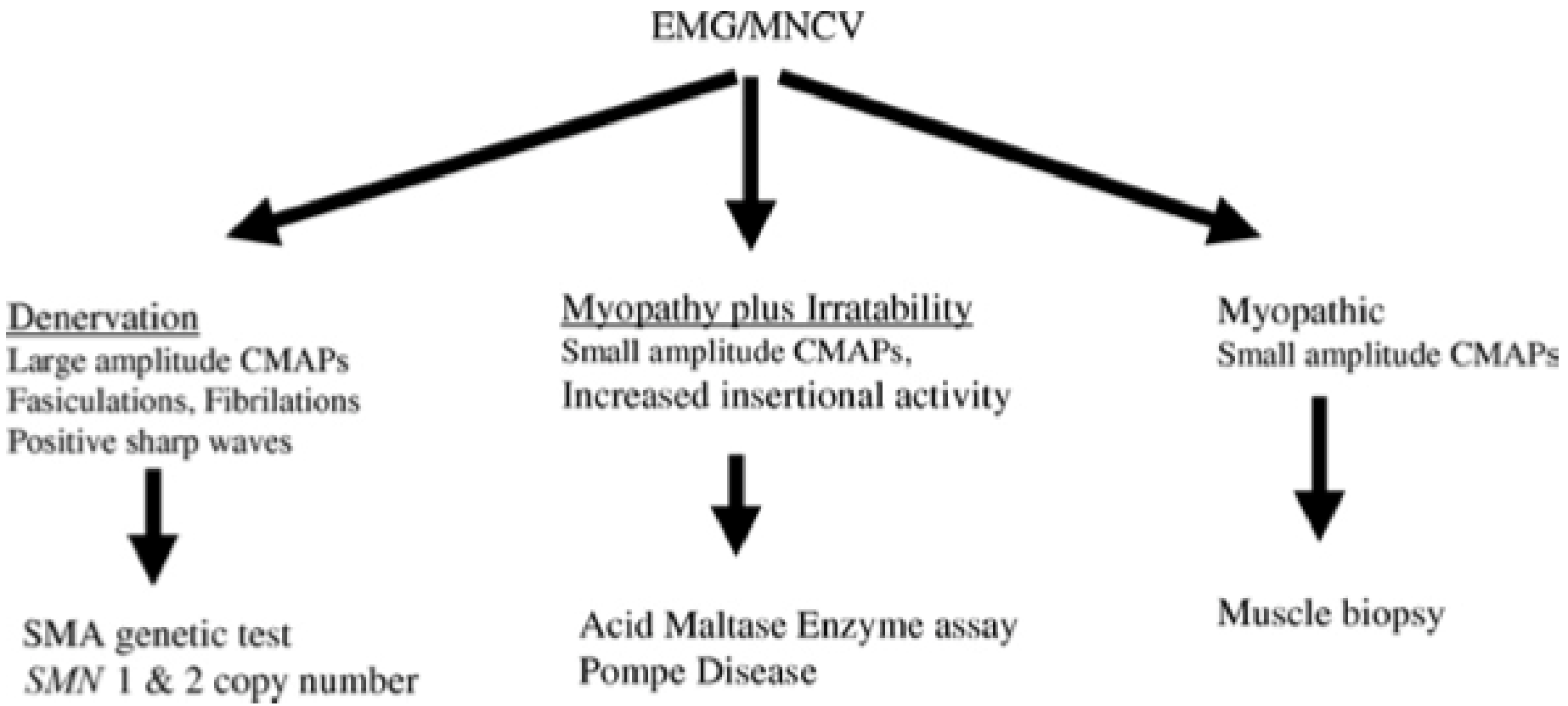


Figure 3 Evaluation of motor unit hypotonia.

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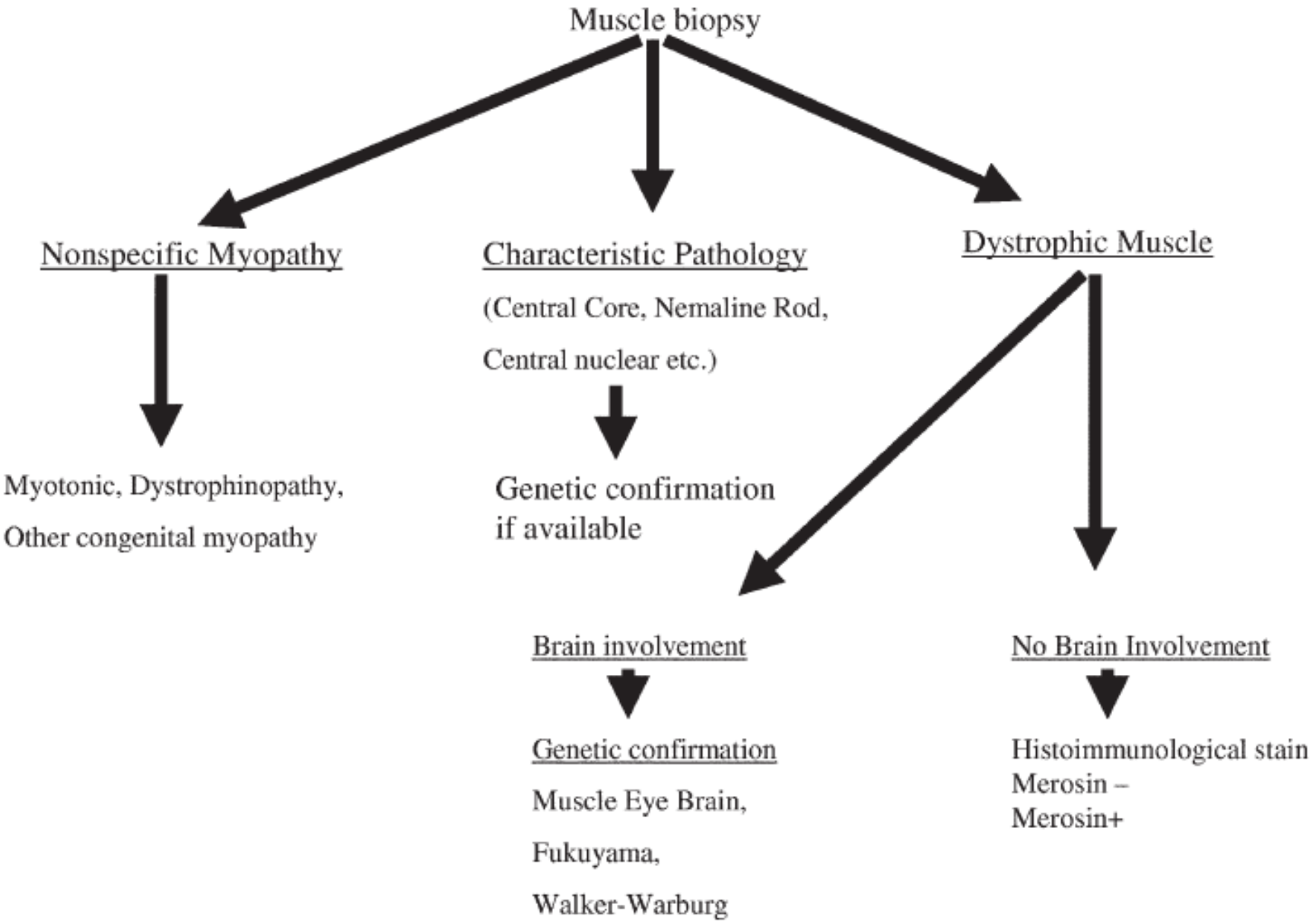

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Site of involvement	Deep tendon reflexes	EMG	Muscle biopsy
Central	Normal or increased	Normal	Normal
Anterior horn cell	Absent	Fasciculation / fibrillation	Denervation pattern
Peripheral nerve	Decreased	Fibrillation	Denervation pattern
Neuromuscular junction	Normal	Decremental / incremental	Normal
Muscle	Decreased	Short duration small amplitude potential	Characteristic




THANK YOU

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