APPROACH TO HYPOTONIA

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CHILD NEUROLOGIST

INTRODUCTION

- ***Tone :*** is defined as the resistance to passive movement.

Muscular tone is conventionally separated into phasic and postural types.

- ***Phasic tone*** is the result of rapid stretching of a tendon, attached muscle, and most importantly, the muscle spindle. The response is rapid and short-lived.
- ***Postural tone*** is the result of a steady, restrained stretch on tendons and attached muscles, with resultant protracted contraction of the involved muscle. Gravity is the most common stimulus for this response.

Swaiman"s pediatric Neurology : practice and principles 5th edition

- **Hypotonia** is decreased resistance to passive movement.
- **Hyperextensibility** of the elbows, wrists, knees, and ankles usually accompanies hypotonia but is not pathognomonic.
- The term "**floppy**" is frequently used to describe hypotonic infants

Swaiman"s pediatric Neurology : practice and principles 5th edition

- It is important to distinguish weakness from hypotonia.

- Weaknessis reduction in the maximum power that can be generated
- Weak infants always have hypotonia, but hypotonia may exist without weakness.

Swaiman"s pediatric Neurology : practice and principles 5th edition

PATHOLOGY

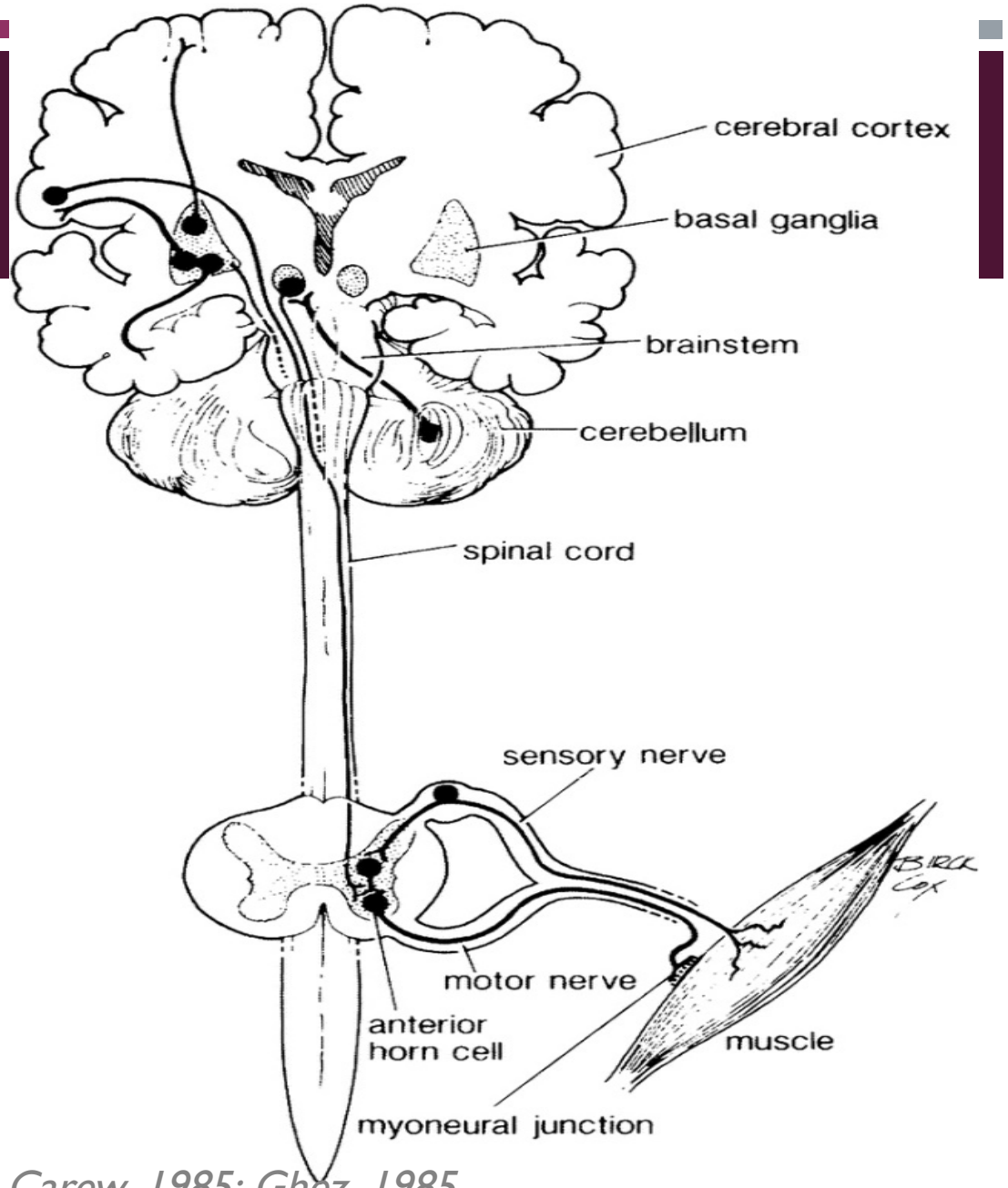
- The central and peripheral nervous systems modify tone, but intrinsic physical characteristics of the tendons, joints, and muscles and the anatomic interrelationships of these structures also contribute significantly to tone.

M.H. Brooke, J.E. Carroll, S.P. Ringel: Congenital hypotonia revisited [Review]. Muscle Nerve. 2:84 1979

- The final common pathway of upper or lower motor unit modification of tone is through the gamma loop (fusimotor) system.

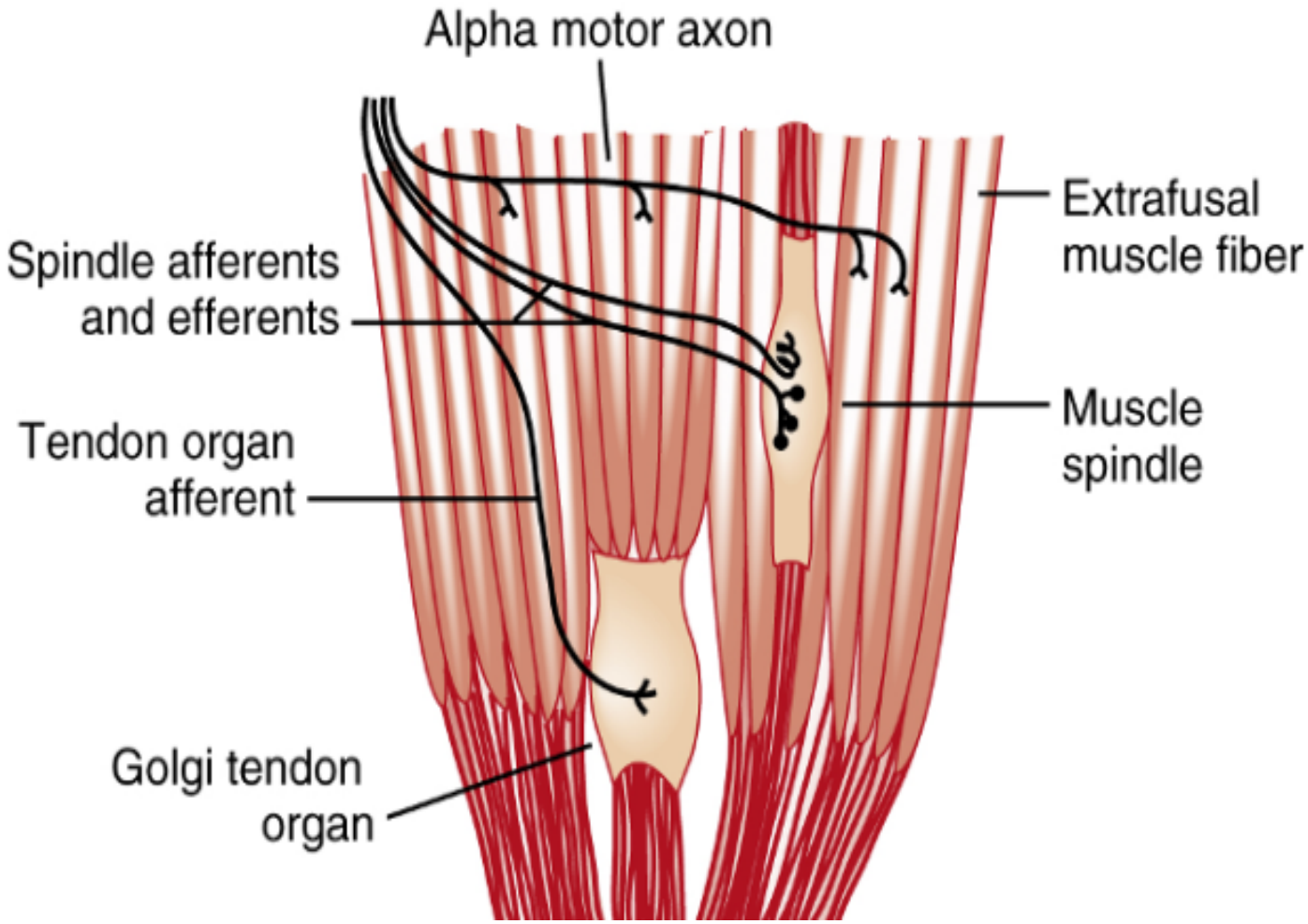
Gordon and Ghez, 1991; Granit, 1975

Through the effect on the gamma motor neuron that portions of the CNS (i.e., motor cortex, basal ganglia, vestibular nuclei, reticular formation, and cerebellum) modify tone, with ensuing hypotonia or hypertonia (i.e., spasticity)



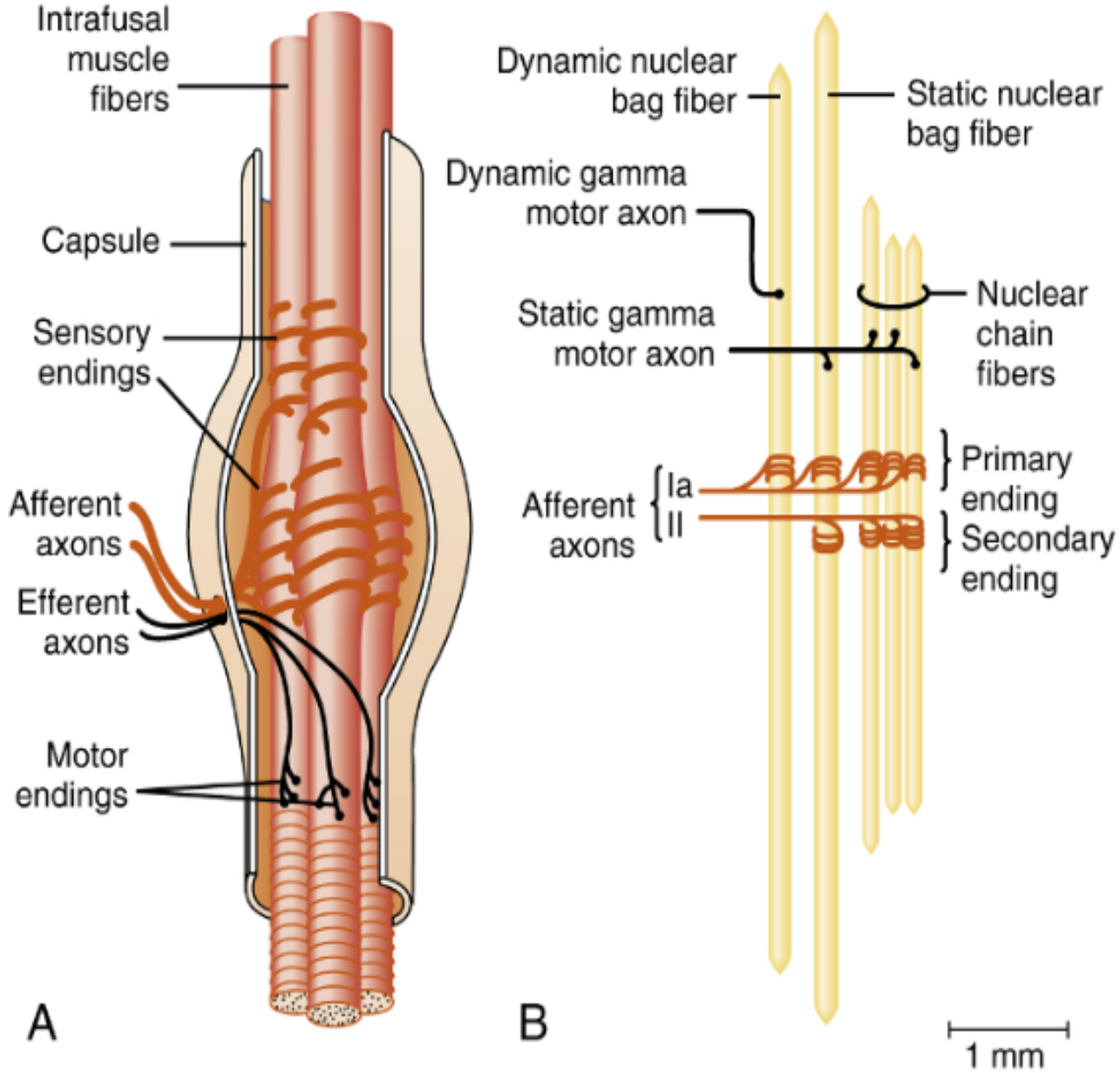
Alexander and Delong, 1985; Brooks and Stoney, 1971; Carew, 1985; Ghez, 1985

- Intimately involved with monitoring and effecting tone are the two stretch-sensitive muscle receptors – the muscle spindles and the Golgi tendon organs
- It also has become evident that nonreflex, mechanical mechanisms are involved in the maintenance of resting muscle tone



R.A. Davidoff: Skeletal muscle tone and the misunderstood stretch reflex. Neurology. 42:951 1992 1579249

- Sensory endings wrap around the central sections of the intrafusal fibers and monitor the stretch of these fibers.
- Through efferent axons, gamma neurons within the anterior horn of the spinal cord innervate the contractile muscle portions on each end of the intrafusal fiber and enhance the sensitivity of the sensory endings to stretch



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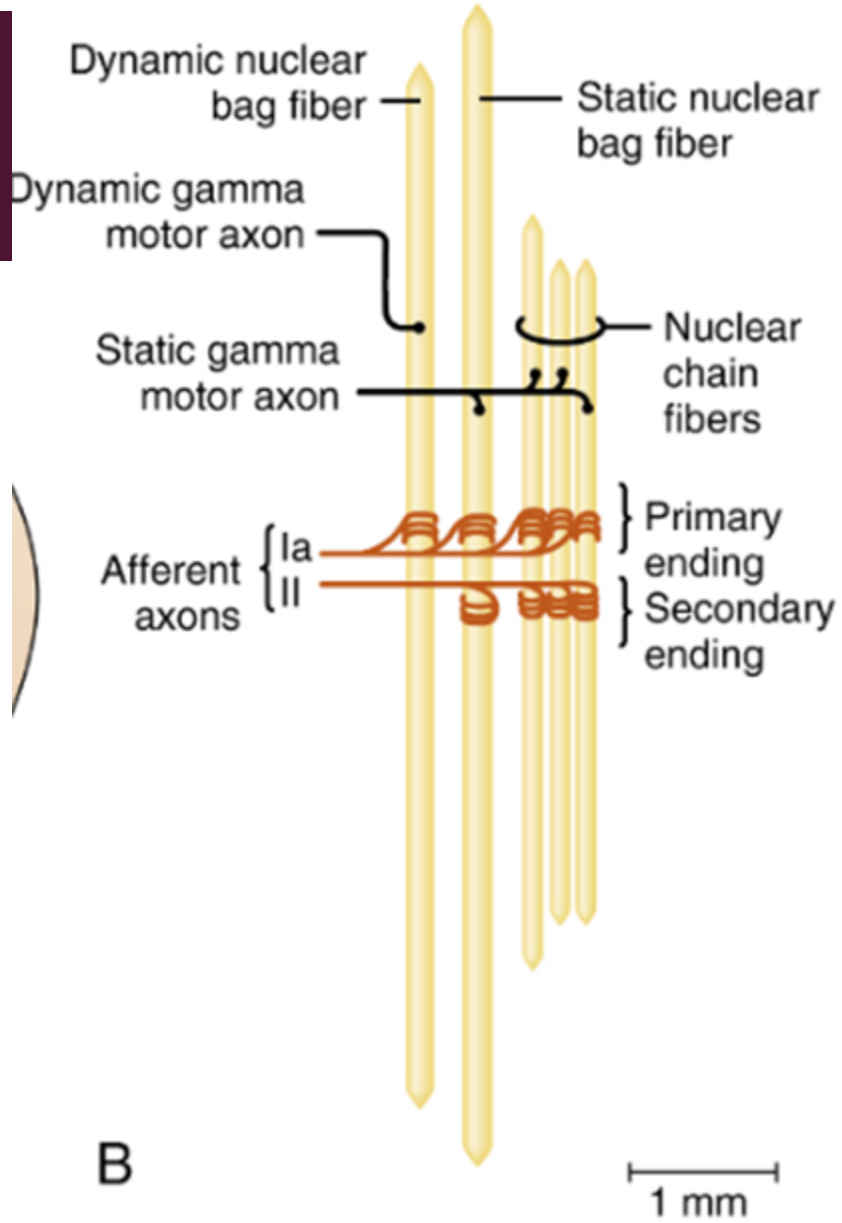
- The intrafusal muscle fibers are divided into three types: nuclear chain fibers, dynamic nuclear bag fibers, and static nuclear bag fibers
- The various sensory endings on the different types of intrafusal fibers have different sensitivities to rate of change of length
- This intricate system of muscle spindle innervation allows the muscle stretch receptors to monitor muscle tension, length, and velocity of stretch, and provide input for maintenance of tone.



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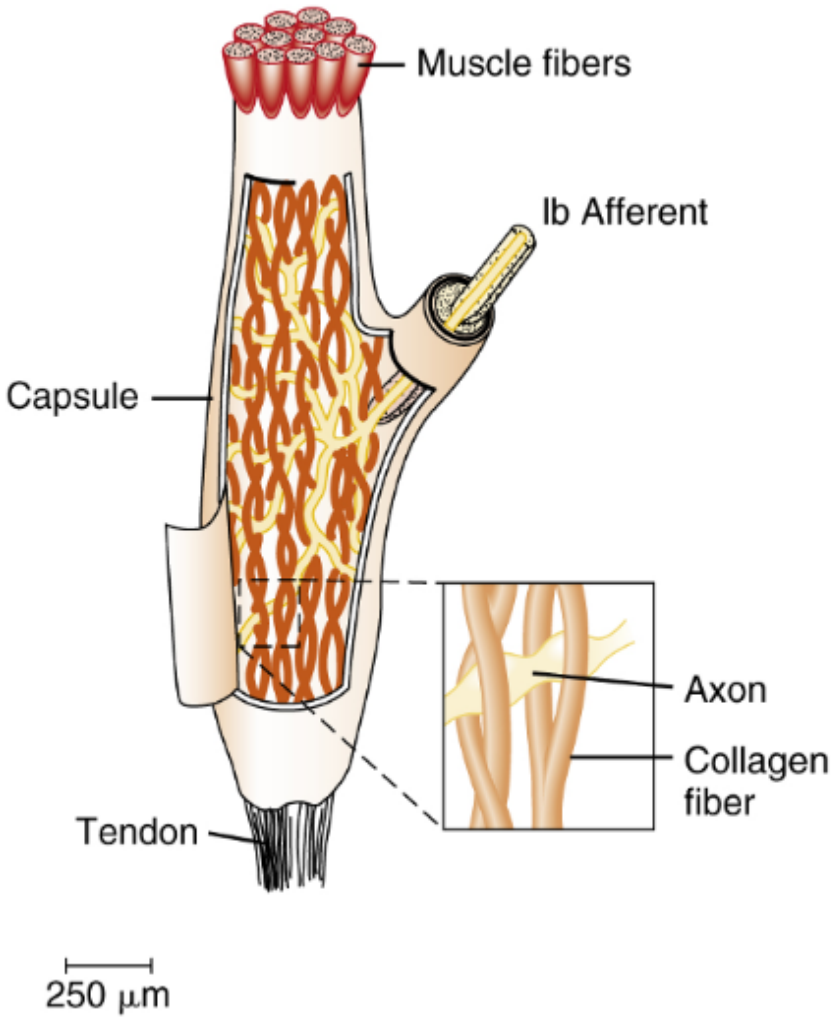
- The Golgi tendon organs, unlike the muscle spindles, are found in series with the skeletal muscle fibers, and are attached at one end to the muscle and at the other to the tendon.
- The afferent axon branches are compressed when muscle contraction occurs and impulses are transmitted.



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EVALUATION OF THE PATIENT

History :

- The *age* at which hypotonia is first evident may be diagnostically crucial.
- The prenatal history should include information on fetal movement in utero, fetal presentation, and the amount of amniotic fluid present
- Maternal exposures to toxins or infections suggest a central cause.
- Low Apgar scores may suggest floppiness from birth, and a hypotonic newborn should be considered septic until proven otherwise.
- A term infant who is born healthy but develops floppiness after 12 to 24 hours may have an inborn error of metabolism.

- if the hypotonia is fluctuating, static, or progressive
- Acute onset of progressive, profound weakness and hypotonia in previously normal infants suggests the possibility of infantile botulism.
- Hx of seizure
- Development …….
- In addition, the child who has hypotonia may exhibit oral-motor dysfunction, poor respiratory support, weak cry and gastroesophageal reflux.

- A careful family history must be sought because several conditions characterized by hypotonia are hereditary

- In a retrospective review of hypotonic infants reported a family history of neuromuscular or neurologic disorders in almost half

K. Birdi, A.N. Prasad, C. Prasad, et al.: The floppy infant: retrospective analysis of clinical experience (1990–2000) in a tertiary care facility. J Child Neurol. 20:803 2005

Examination :

- The physical examination should include the assessment of pertinent clinical features, an assessment for dysmorphic features and a comprehensive neurologic evaluation…

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The Floppy Infant : Evaluation of Hypotonia

- The finding of fixed ***contractures*** in the neonatal period suggests that hypotonia is associated with primary disorder of bone or muscle or an antenatal insult

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- The infant's tendency to assume unusual postures may indicate the presence of hypotonia – especially the "frogleg" position, in which the supine infant lies with the lower limbs externally rotated and abducted.

- Plagiocephaly frequently is present

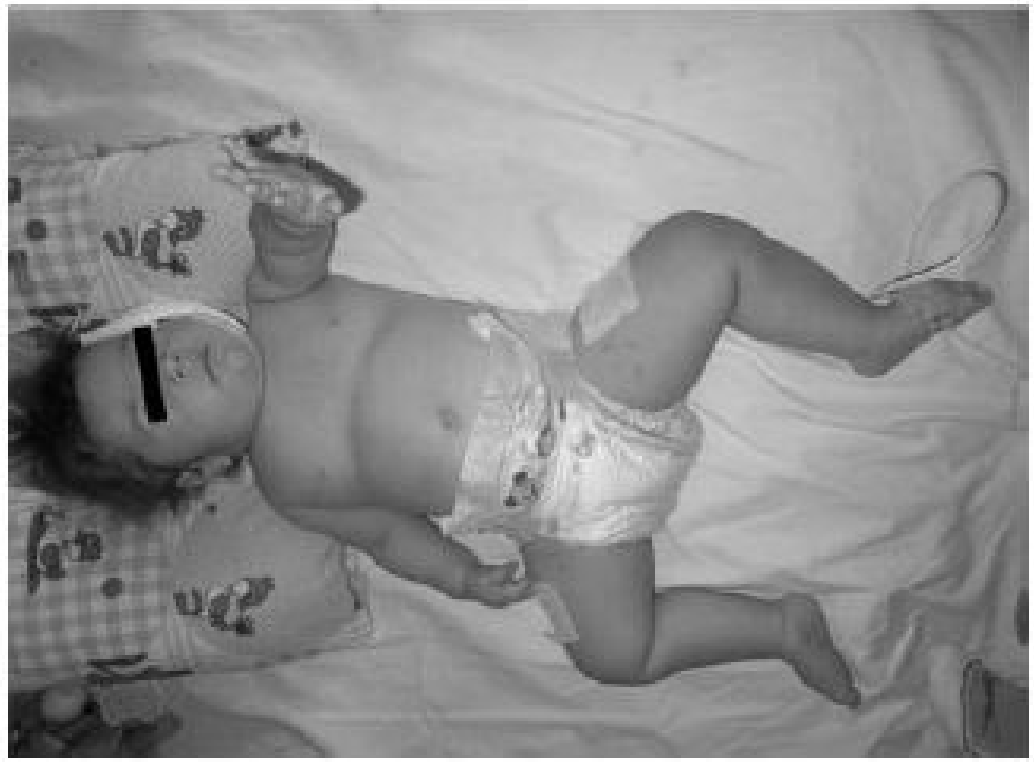

Fig. 1. Hypotonia, frog-like position and obesity of the

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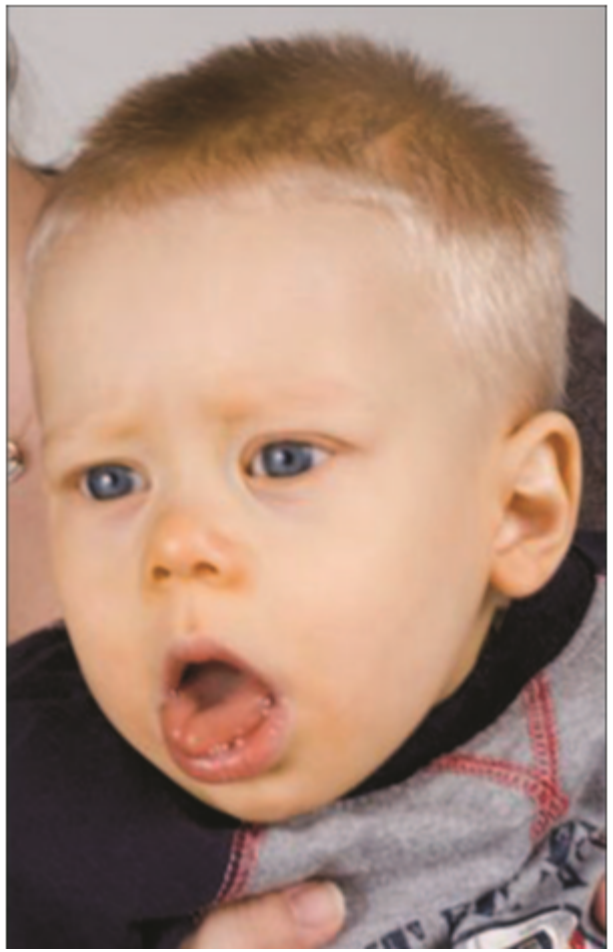
- Weakness of facial muscles, weakness of muscles necessary for adequate suck and swallow, and paresis of the eyelid levators and extraocular muscles are often associated with genetic myopathies



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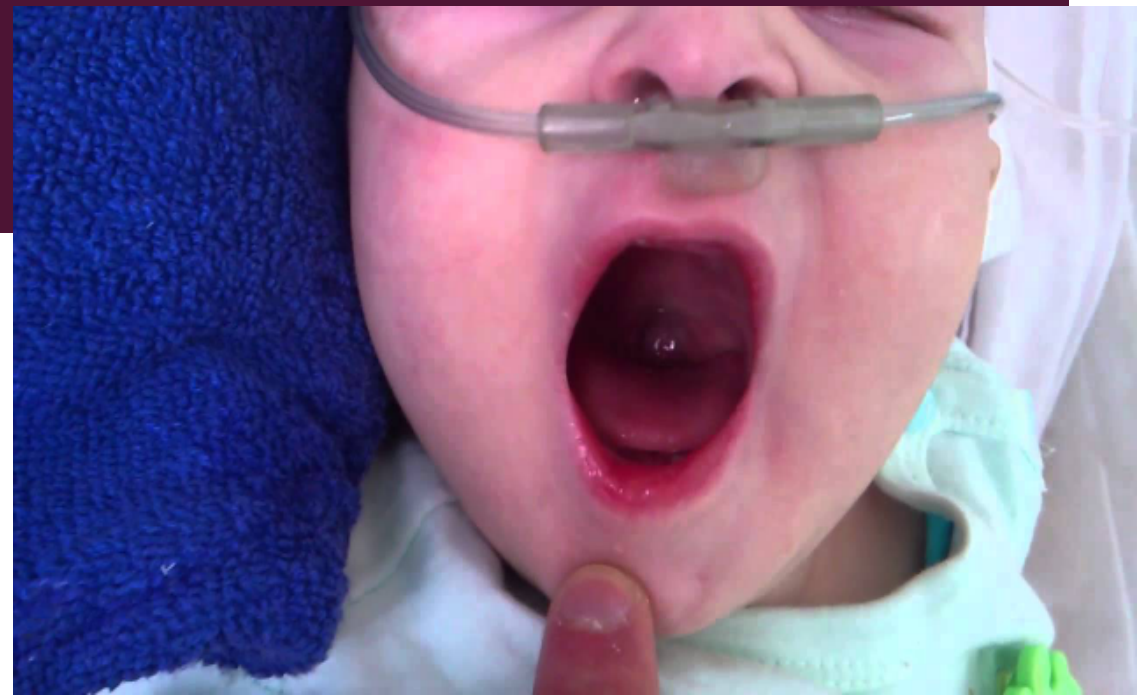
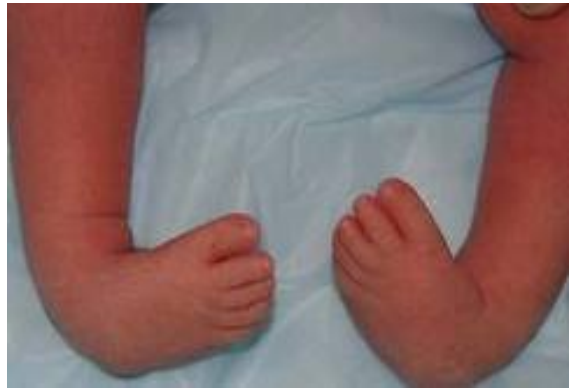


- The tongue should be carefully examined for atrophy and fasciculations

- Older children may present with talipes planus, pronation at the ankles, and genu recurvatum



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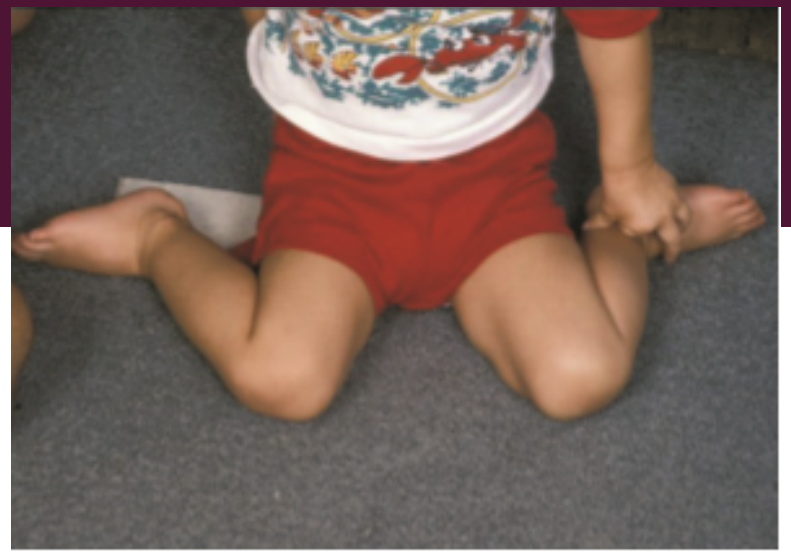
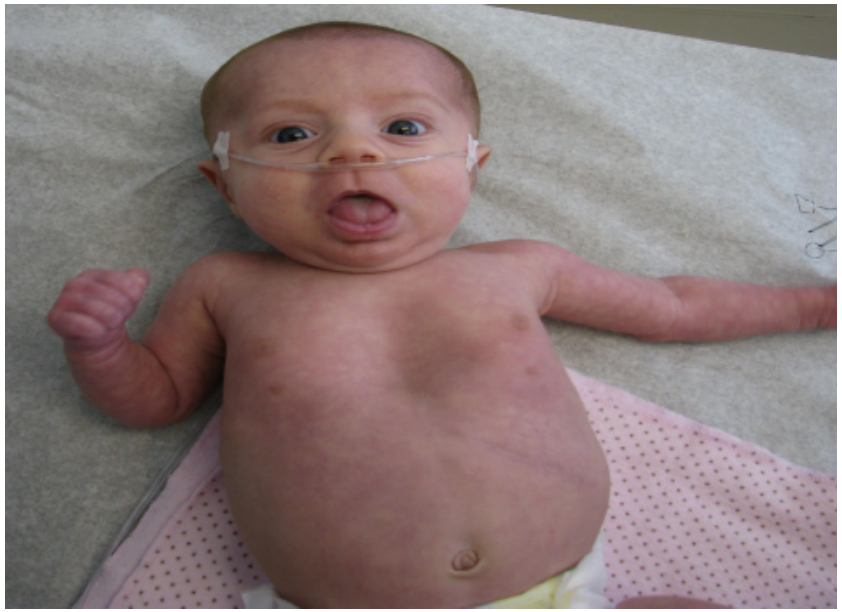


- Abnormalities in stability and movement may manifest in an older infant as a combat crawl, W-sitting

- The pectus excavatum deformity and a bell-shaped chest indicate relative weakness of intercostal muscles



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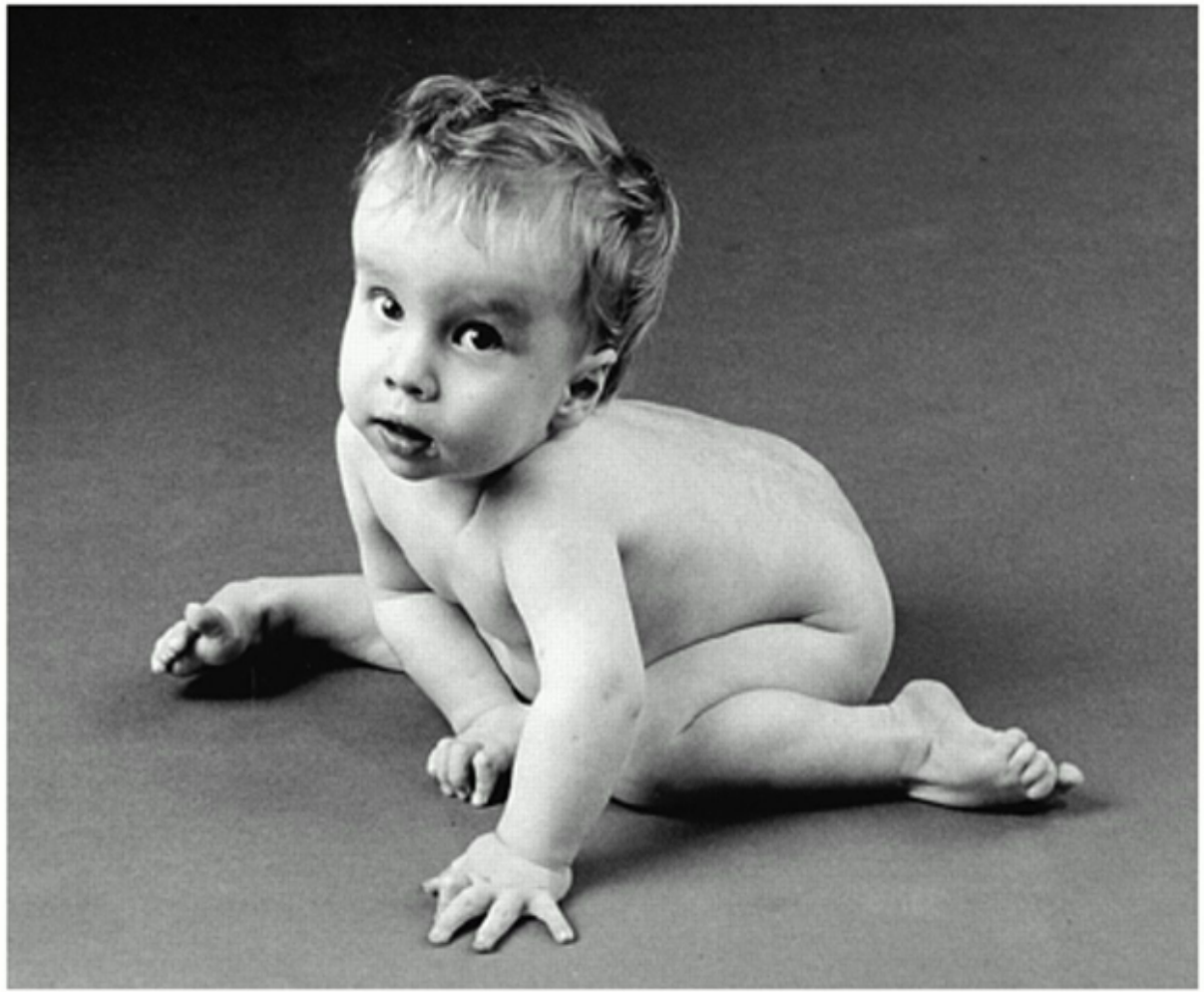
- poor trunk extension, astasias (inability to stand due to muscular incoordination)



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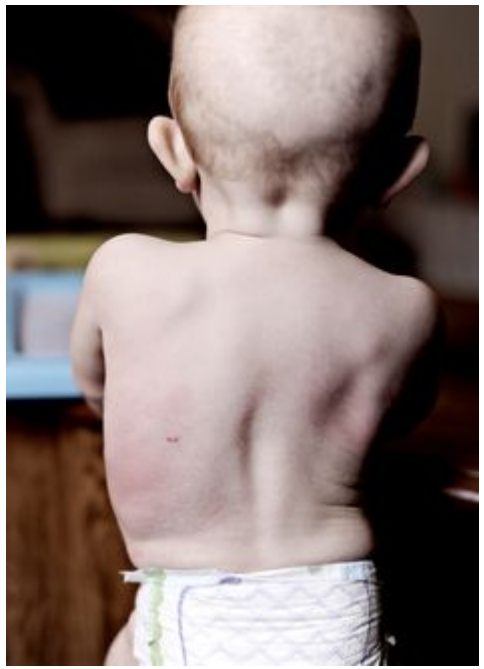
- the ambulatory child may manifest with a waddling gait
- The presence of scoliosis suggests associated weakness and neuromuscular disease.



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- A detailed neurologic assessment examining tone, strength, reflexes, muscle bulk and sensation.

- To assess the tone :
- Horizontal suspension : U shape

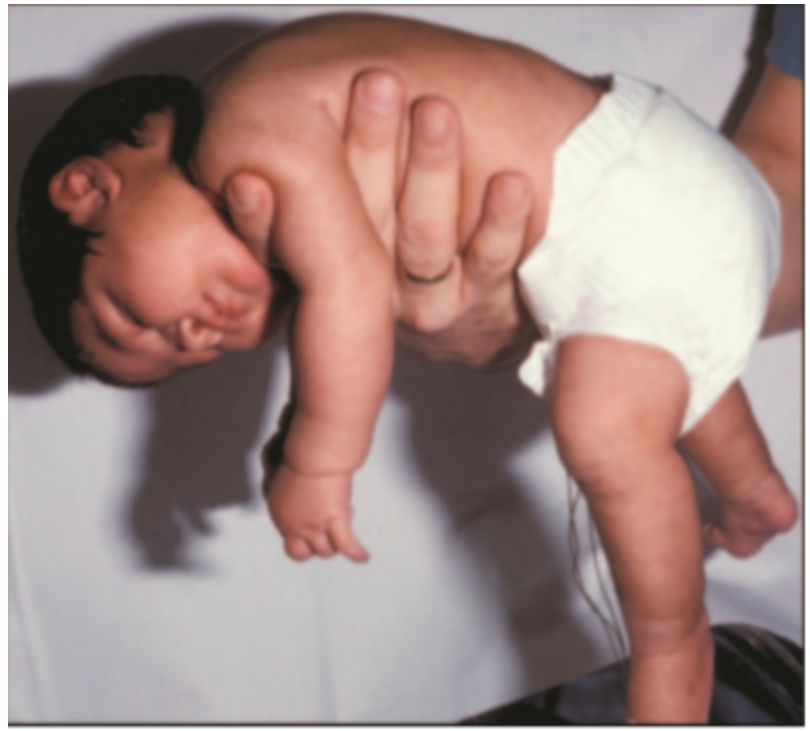

Figure 1. Infant who has trisomy and hypotonia, showing "U" posture with horizontal suspension.

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- vertical suspension : “slips through” at the shoulders when the examiner grasps him or her under the arms in an upright position
- Head lag or hyperextension is evident when the infant is pulled by the arms from as up into sitting position (traction)

igure 3. A 15–month–old boy who has developmental delay nd hypotonia, as evidenced by significant head lag with raction.

Figure 2. A 2–year–old girl who has developmental delay and

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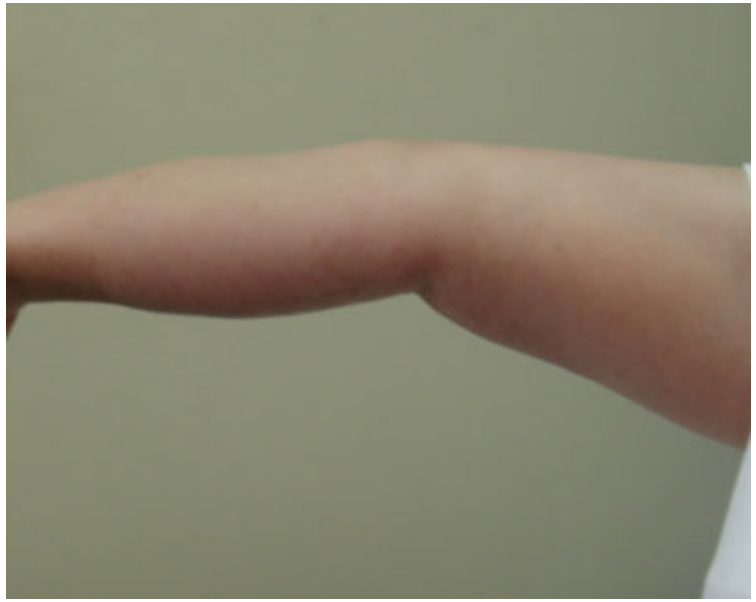
- Passive pronation, supination, flexion, and extension of the limbs and gently shaking the hands and feet are the best ways to assess tone.
- Often, in the hypotonic infant, the elbows, wrists and fingers can be extended beyond their normal range



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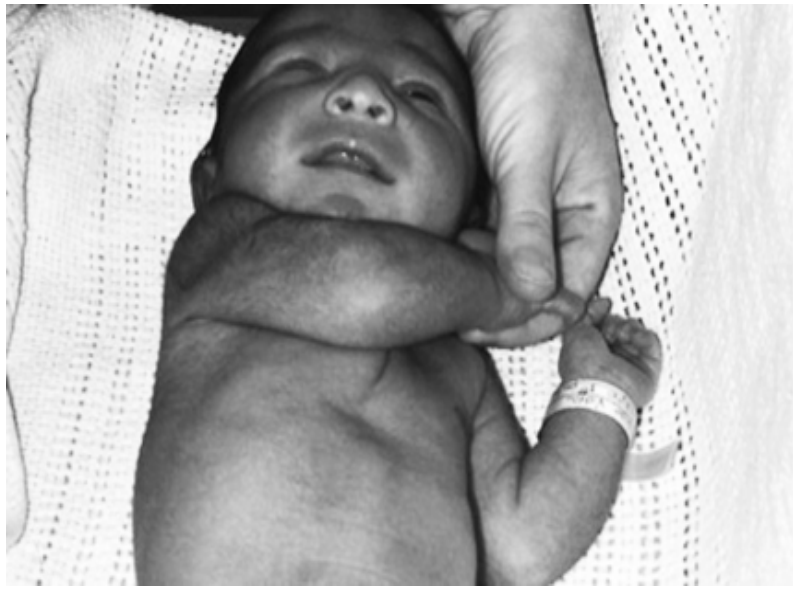
- The scarf sign involves wrapping the infant's arm across the chest toward the neck on the contralateral side and is positive when the elbow can be readily moved beyond the midline



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- The hypotonic infant's foot can be brought to the opposite ear, and extreme passive foot dorsiflexion may be possible when hypotonia is profound.

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- Power must be assessed in all patients

- If limb weakness is present, localization of the weakness to the proximal or distal extremities should be attempted

- Fasciculations of limb muscles are difficult to observe in infants because of abundant subcutaneous tissue. However, the experienced examiner can usually palpate the underlying muscle beneath the fat and estimate the adequacy of muscle bulk.

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- Deep tendon reflexes and plantar reflexes should always be elicited at all ages.

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DIFFERENTIATING CENTRAL VERSUS PERIPHERAL CAUSES

- The upper motor neuron (unit) includes the pyramidal neuron in the motor cortex and the myelinated nerve fiber, which traverses the corticospinal tract and eventually terminates in the internuncial pool in the spinal cord adjacent to the anterior horn cell.
- The lower motor neuron (unit) consists of the anterior horn cell, peripheral nerve, neuromuscular junction, and muscle.
- Combined disorders also occur.

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- Several studies have shown that central causes account for 60% to 80% of hypotonia cases and that peripheral causes occur in 15% to 30%.

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CLUES FOR CENTRAL HYPOTONIA

- Do not track visually, fail to imitate facial gestures, or appear lethargic, depressed level of consciousness, normal strength with hypotonia, and hyperactive or normal reflexes.
- Abnormalities of brain function, dysmorphic features, fisting of the hands, scissoring on vertical suspension, and malformations of other organs
- early seizures, abnormal eye movements, apnea, or exaggerated irregular breathing patterns

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PERIPHERAL HYPOTONIA

- If a hypotonic infant is alert, responds appropriately to surroundings, and shows normal sleep-wake patterns, the hypotonia likely is due to involvement of the peripheral nervous system
- Peripheral causes are associated with profound weakness in addition to hypotonia and hyporeflexia or areflexia
- also are associated with muscle atrophy, lack of abnormalities of other organs, the presence of respiratory and feeding impairment, and impairments of ocular or facial movement

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Variable	Central Injury	Central Developmental	Anterior Horn Cell	Peripheral Nerve	Neuromuscular Junction	Muscle
Strength	Normal or slight weakness	Normal or slight weakness	Weakness	Weakness	Weakness	Weakness
Deep tendon reflexes	Normal to increased	Normal	Decreased	Decreased	Normal to decreased	Decreased to absent
Babinski sign	+/−	+/−	Absent	Absent		
Infantile reflexes	Persistent	Persistent/Absent	Absent	Absent	Absent	Absent
Muscle fasciculations	Absent	Absent	Prominent	Absent	Absent	Absent
Muscle mass	Normal or disuse atrophy	Normal or disuse atrophy	Prominent atrophy (proximal)	Distal atrophy	Normal or decreased	Proximal atrophy; increased or decreased distal pseudohypertrophy
Sensation	Normal	Normal	Normal	Increased or decreased	Normal	Normal
Tone	Decreased evolving to increased	Decreased	Decreased	Decreased	Decreased or normal	Decreased

- Diseases of the upper motor unit may be classified according to pathophysiologic cause (i.e., metabolic, degenerative, traumatic, congenital-structural, infectious, or toxic).
- A similar classification may be used for lower motor unit diseases; such diseases also may be categorized by the anatomic site of involvement

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Upper Motor Unit Disease (Central Nervous System Diseases)

- Acute cerebral insult
- Cerebrovascular accident (e.g., hemorrhage, thrombosis, embolism)
- Hypoxic-ischemic encephalopathy
- Infection (e.g., viral, bacterial, fungal, parasitic)

Chromosomal abnormality

- Angelman's syndrome
- Down syndrome
- Prader–Willi syndrome

Congenital motor disease (cerebral palsy)

- Ataxia
- Atonic diplegia or paraplegia (periventricular leukomalacia)

Incontinentia pigmenti

Metabolic disease

- Carnitine deficiency
- Cytochrome c oxidase deficiency
- Fucosidosis
- Gangliosidosis (GM1)
- Hyperammonemia
- Hypercalcemia . Hyperglycinemia
- Hyperlysinemia
- Mannosidosis
- Niemann–Pick disease
- Oculocerebrorenal syndrome (Lowe's syndrome)
- Organic acidemias
- Renal tubular acidosis
- Tay–Sachs disease (and other GM2 gangliosidoses)

Toxicity

- Bilirubin
- Magnesium
- Phenobarbital / Phenytoin
- Sedative drugs

Trauma

- Brain
- Cord

Lower Motor Unit (Peripheral Nervous System Diseases)

- Arthrogryposis multiplex congenita
- Carnitine deficiency
- Connective tissue disease, such as Ehlers–Danlos syndrome

Anterior horn cell

- Infantile spinal muscular atrophy
- Kugelberg–Welander disease
- Poliomyelitis

Peripheral nerve

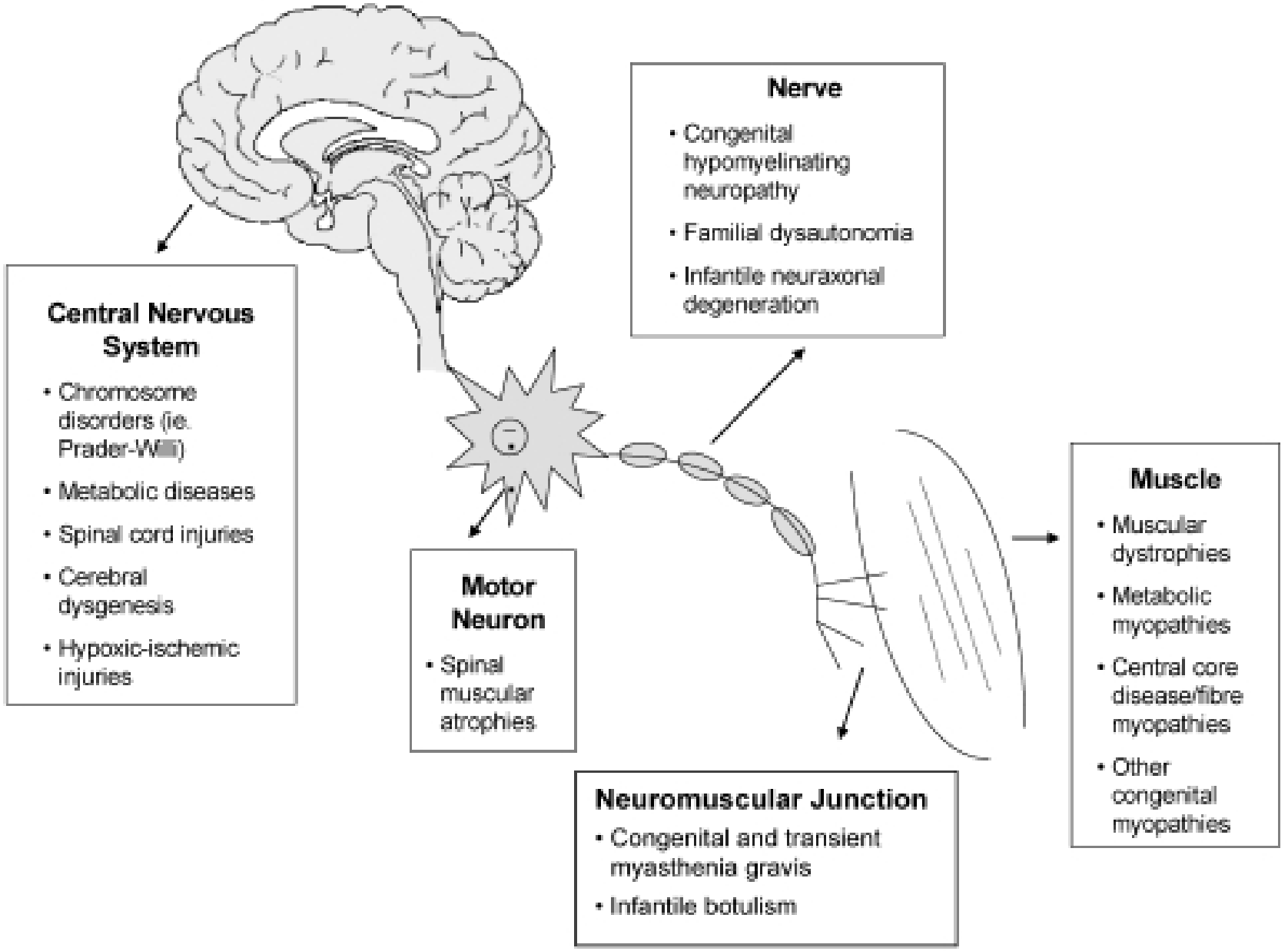
- Familial dysautonomia
- Guillain–Barré syndrome
- Hereditary motor-sensory neuropathies
- Polyneuropathy

Neuromuscular junction

- Botulism
- Myasthenia gravis
- Myasthenic syndrome
- Neonatal myasthenia gravis (immune- and nonimmune-mediated forms)
- Neonatal transient myasthenia gravis

Muscle

- Congenital myopathies (e.g., central core disease, congenital fiber type disproportion, myotubular myopathy, nemaline myopathy)
- Glycogen storage disease (e.g., acid maltase deficiency, phosphofructose kinase deficiency, phosphorylase deficiency)
- Hypothyroidism
- Myotonic dystrophy
- Polymyositis


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

Cause of Hypotonia	Hypotonic Series (n=277)	Prevalence	Distinguishing Features	Test Available?
Hypoxic–ischemic Encephalopathy	19%			
Genetic/Chromosomal Syndromes	31%			
Down syndrome	13%	1:800 to 1:1,000		Karyotype
Prader–Willi syndrome	5%	1:10,000 to 1:30,000		Methylation
Other dysmorphic syndromes	9%			
Other chromosomal anomalies	4%			Karyotype
Fragile X syndrome		1:4,000 males 1:8,000 females		*FMR1* test
Trisomy 18 (Edwards syndrome)		1:5,000 to 1:6,000		Karyotype
1p36 deletion syndrome		1:5,000 to 1:10,000		Array CGH
22q13 deletion syndrome		•		Array CGH
22q11.2 deletion syndrome (velocardiofacial/DiGeorge syndrome)		1:4,000 to 1:6,400		Array CGH
Williams syndrome		1:7,500		Array CGH
Trisomy 13 (Patau syndrome)		1:10,000		Karyotype
Smith–Magenis syndrome		1:15,000 to 1:25,000		Array CGH
Sotos syndrome		1:14,000		Array CGH
Wolf–Hirschhorn syndrome		1:50,000		Array CGH
Kabuki syndrome		1:30,000		None
Cri du chat syndrome		1:20,000 to 1:50,000		Karyotype
Brain anomalies	13%			

Myopathies	5%			
Central core disease		**		
Nemaline myopathy		1:50,000		
X-linked myotubular myopathy		1:50,000		
Congenital myotonic dystrophy	4%	1:100,000		
Metabolic disorders	3%			
Peroxisome biogenesis disorders, Zellweger syndrome spectrum		1:50,000		
Smith-Lemli-Opitz syndrome		1:20,000 to 1:60,000		
Glycogen storage disease Pompe (Type II)		1:14,000 to 1:100,000 1:40,000 (in United States)	Cardiomegaly	GAA gene; Alpha glucosidase
Benign neonatal hypotonia	3%			
Spinal muscular atrophy	2%	1:10,000		
Muscular dystrophies	2%	1:20,000 to 1:40,000		
Joint laxity	1.4%			
Neuropathy	1.4%			
Teratogens	1%			
Brain tumor	0.4%			
Myoclonic encephalopathy	0.4%			
Neuromuscular junction disorder	0.4%			
Familial infantile myasthenia (not transient)		1 to 4.4:1,000,000		Decremental EMG, negative antibodies, multiple gene tests for AcHR
Unknown	13%			

DIAGNOSTIC YIELD

Method of Diagnosis	% Successfully Diagnosed
History and Physical Examination (Step 1) Family history Pregnancy and delivery Clinical and neurologic examination	50%
Imaging Study (CT or MRI/MRS) (Step 2)	13%
Clinical Genetic Evaluation (Step 3)	9%
Genetic Testing (Step 4) Karyotype, FISH, CGH	6%
Biochemical Evaluation (Step 5) Amino acids, organic acids, peroxisomes, carnitine, CDG test	6%
Neuromuscular Testing (Step 6) CK, EMG, NCV, DNA for SMA and CMD, muscle biopsy	6%
Follow-up Testing Some tests repeated/Further tests	7%

LABORATORY EVALUATION

- In hypotonic ***newborn*** work up initially must be directed at **ruling out systemic disorders.**

- Routine studies should include an evaluation *for sepsis* (blood culture, urine culture, cerebrospinal fluid culture)
- measurement of serum electrolytes, including liver functions and ammonia, glucose, calcium, magnesium, and creatinine; a complete blood count; and a urine drug screen

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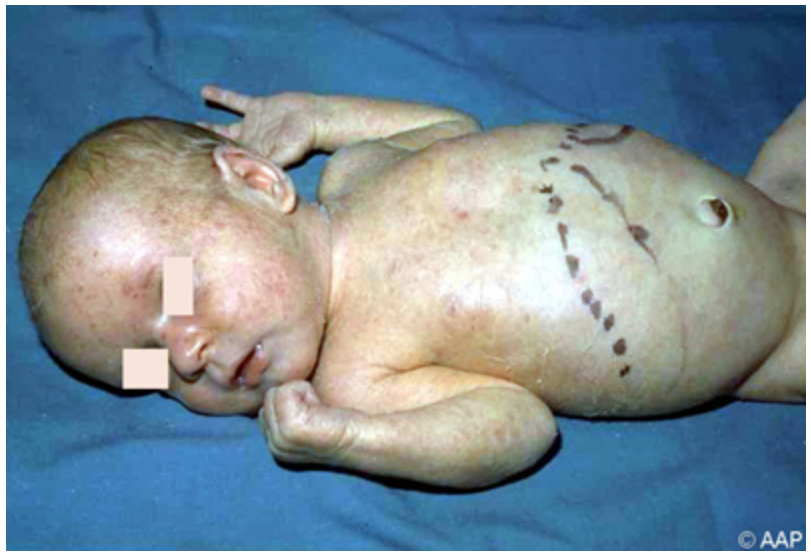
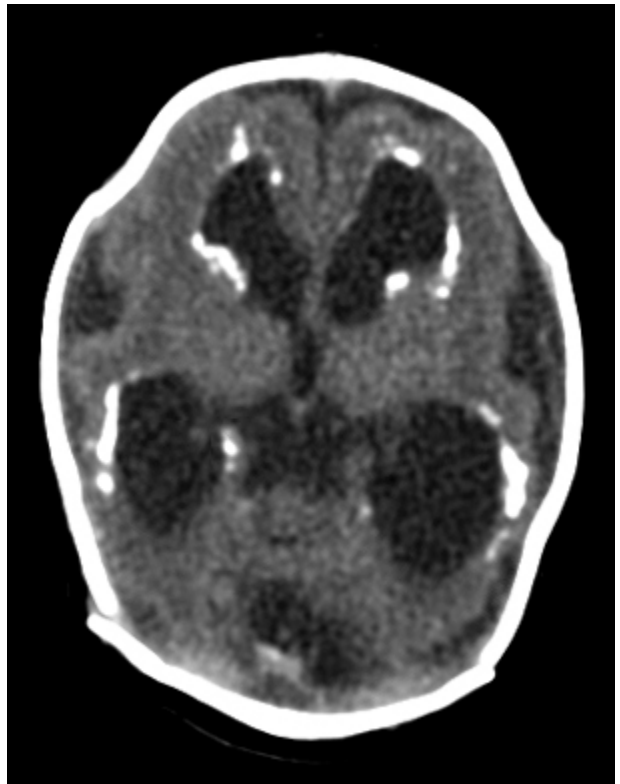
- If hepatosplenomegaly is present and calcifications are noted on head ultrasonography, TORCH titers and a urine culture for cytomegalovirus should be undertaken





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- If the hypotonia is considered to be central, we should evaluate for genetic and metabolic causes …….
- A karyotype is indicated when several significant dysmorphic features are present …
- If the clinical evaluation suggests complex multisystem involvement, screening for inborn errors of metabolism is indicated

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- If acidosis is present, *plasma amino acids and urine organic acids* (aminoacidopathies and organic acidemias), *serum lactate* (disorders of carbohydrate metabolism, mitochondrial disease), *pyruvate,ammonia* (urea cycle defects), and *acylcarnitine profile* (organic acidemia, fatty acid oxidation disorder) should be measured. *Very long-chain fatty acids and plasmalogens* are specific for the evaluation of a peroxisomal disorder.

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- A creatine kinase and acylcarnitine/carnitine concentration should be determined if the child is weak and exhibits hypotonia to aid in diagnosis of a muscular dystrophy or carnitine deficiency

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- To evaluate causes of peripheral hypotonia, creatine kinase concentrations should be measured. This value is elevated in muscular dystrophy but not in spinal muscular atrophy or in many myopathies

- Specific DNA testing can be performed for myotonic dystrophy and for spinal muscular atrophy.

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- Electrophysiologic studies, which show abnormalities in nerves, myopathies, and disorders of the neuromuscular junction. With the exception of a few myopathies, normal EMG findings suggest that the hypotonia is central in origin.

- Muscle biopsy with immunohistochemical staining and electron microscopy is the method of choice for differentiating myopathies and muscular dystrophies

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- If biopsy shows specific abnormalities, it can be an essential part of the diagnostic evaluation in the newborn to guide subsequent DNA molecular diagnostic studies.

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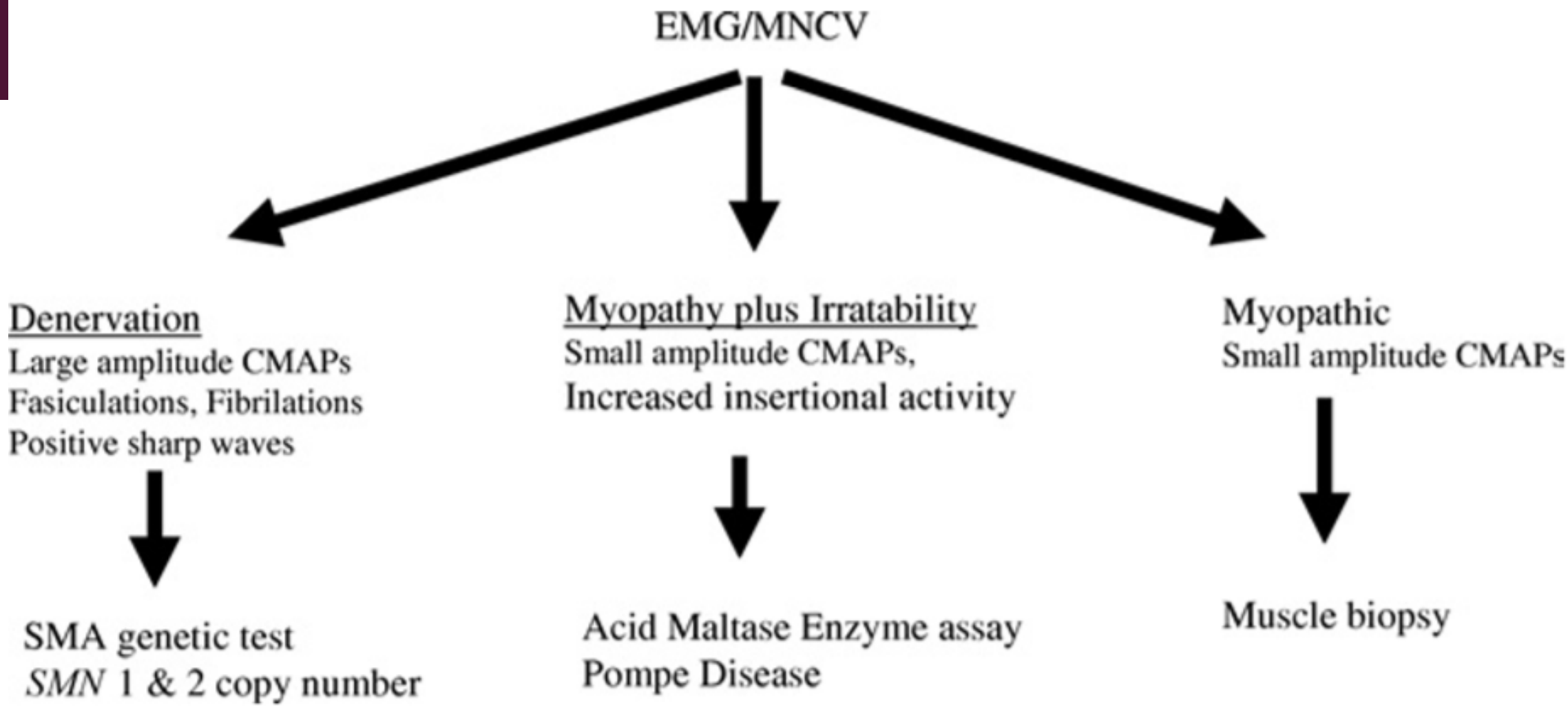
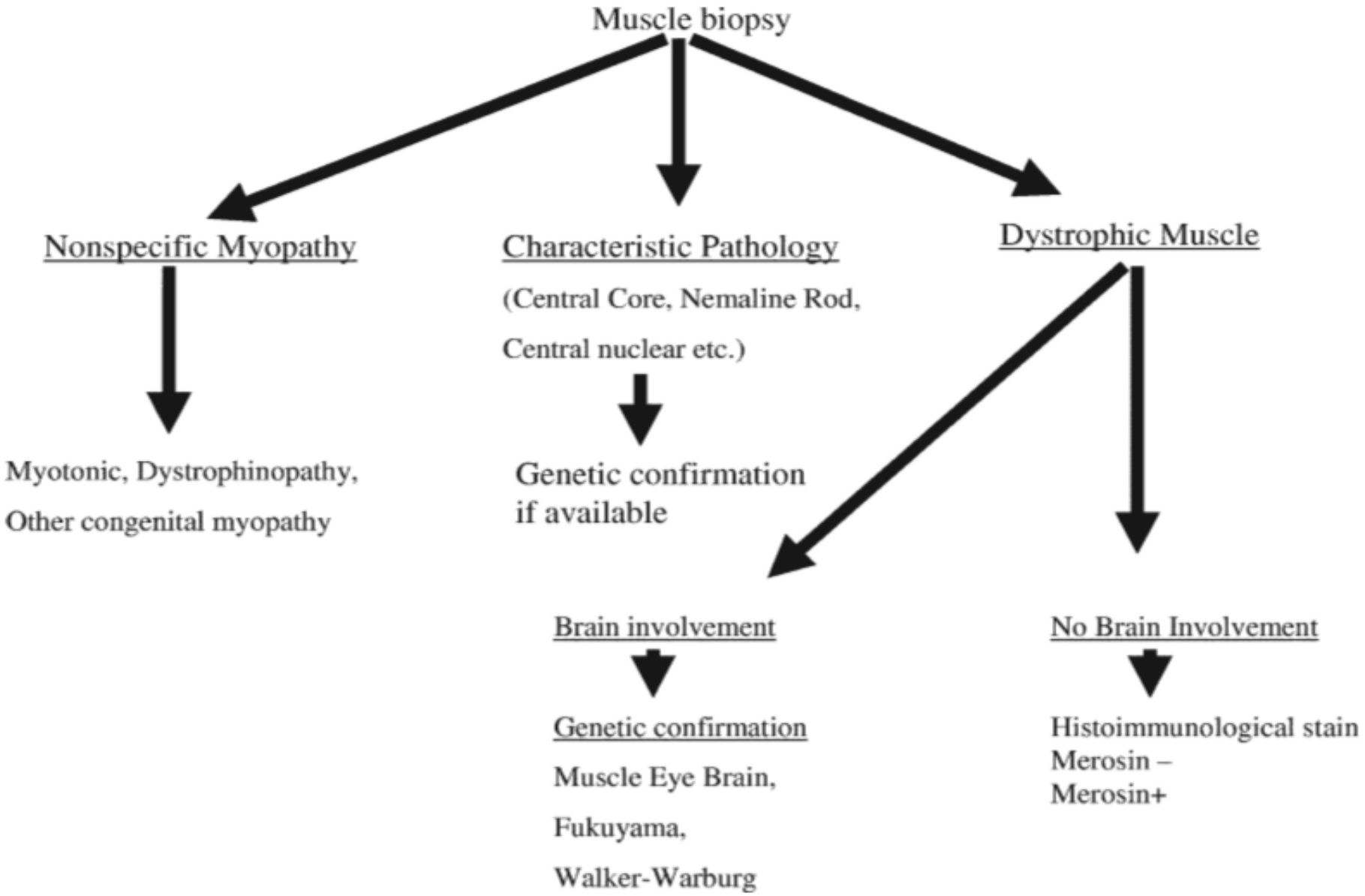
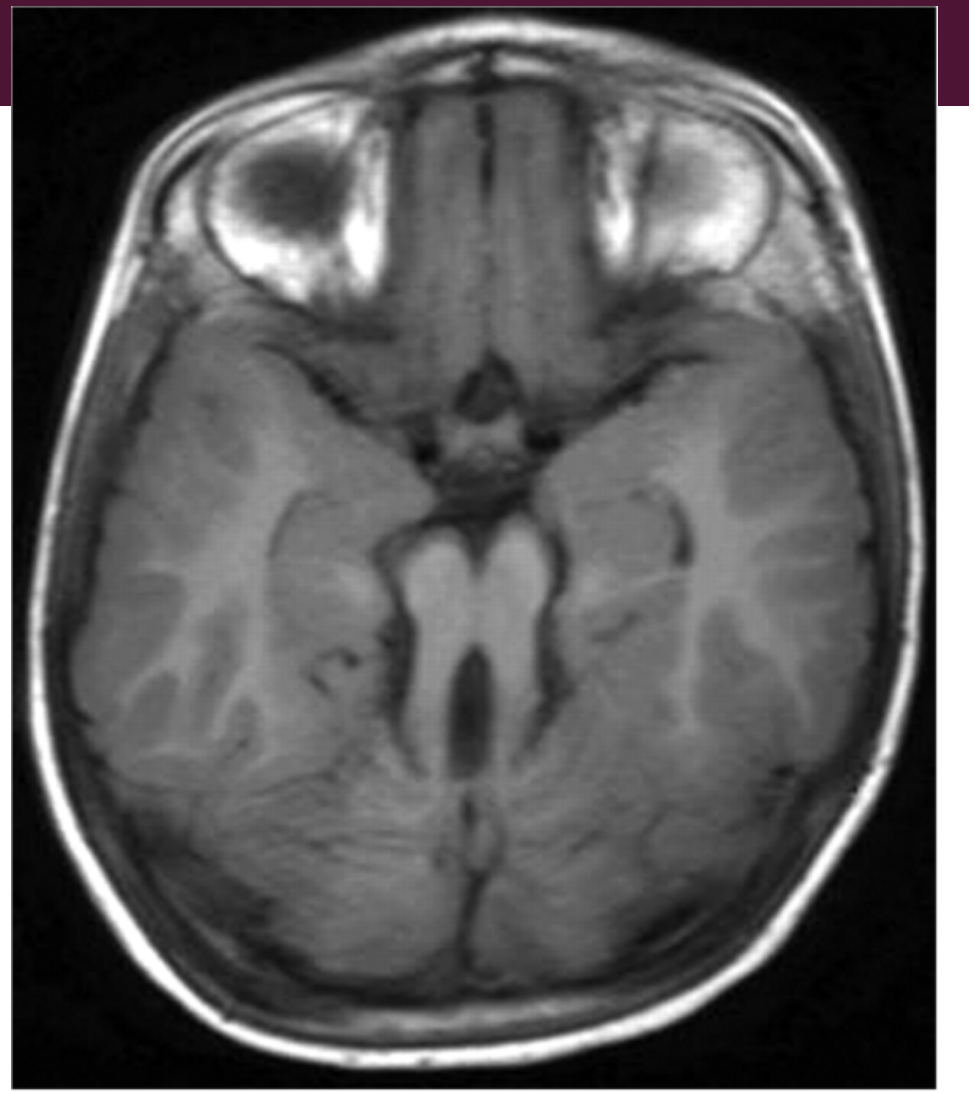

EMG/MNCV
Denervation
Large amplitude CMAPs
Fasiculations, Fibrilations
Positive sharp waves
SMA genetic test
SMN 1 & 2 copy number
Myopathy plus Irratability
Small amplitude CMAPs,
Increased insertional activity
Acid Maltase Enzyme assay
Pompe Disease
Myopathic
Small amplitude CMAPs
Muscle biopsy

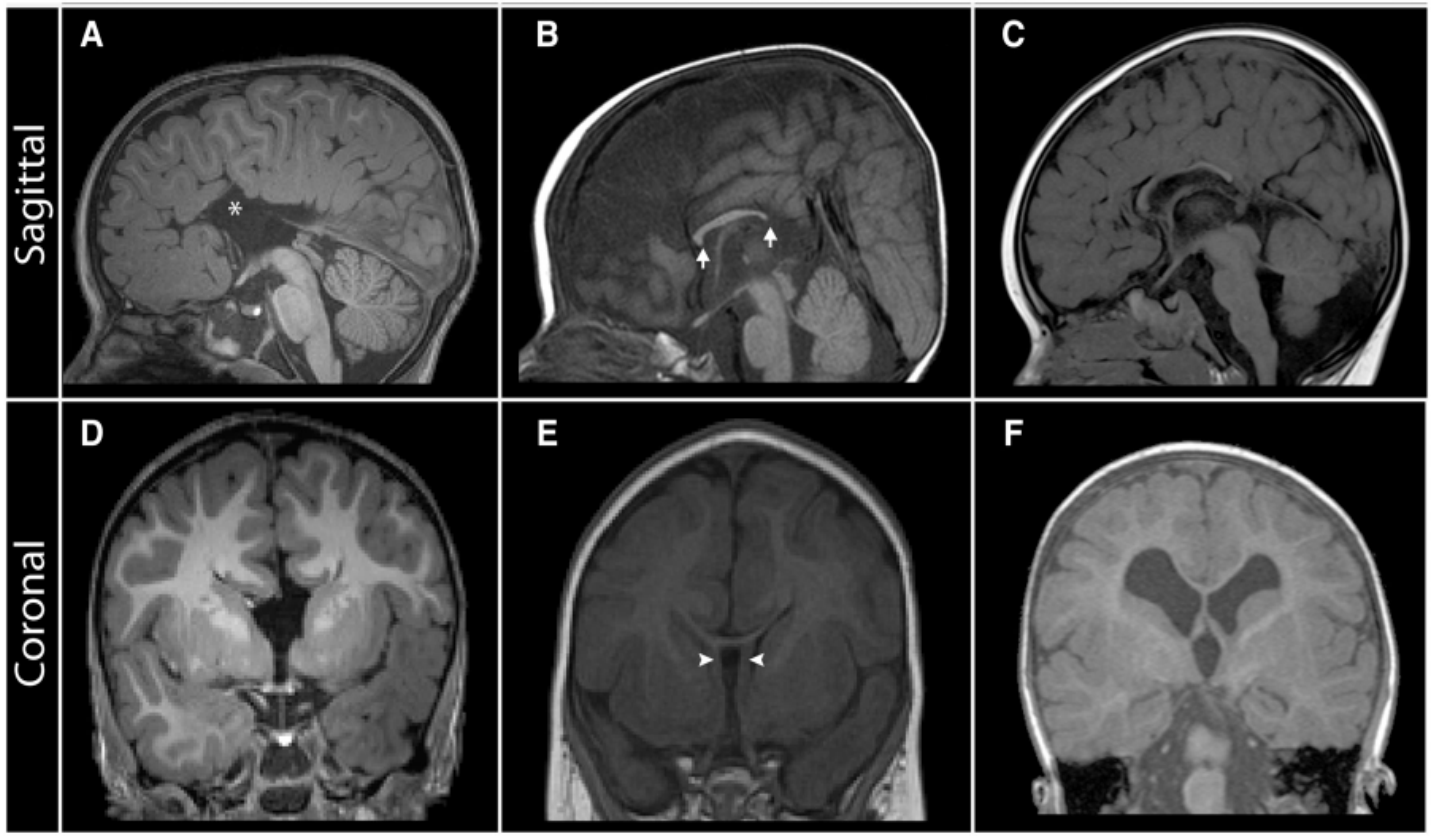

Muscle biopsy
Nonspecific Myopathy
Characteristic Pathology
(Central Core, Nemaline Rod,
Central nuclear etc.)
Dystrophic Muscle
Myotonic, Dystrophinopathy,
Other congenital myopathy
Genetic confirmation
if available
Brain involvement
No Brain Involvement
Genetic confirmation
Muscle Eye Brain,
Fukuyama,
Walker-Warburg
Histoimmunological stain
Merosin –
Merosin+

RADIOLOGIC EVALUATION

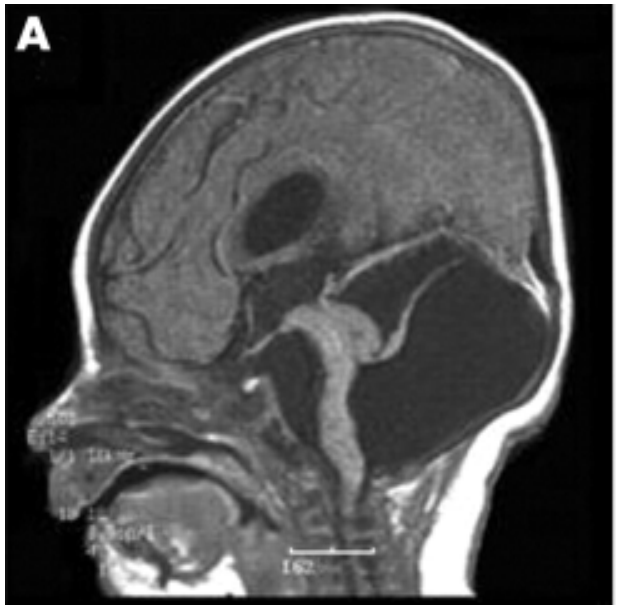
- Magnetic resonance imaging can delineate structural malformations, neuronal migrational defects, abnormal signals in the basal ganglia (mitochondrial abnormalities), or cerebellar defects (Joubert syndrome)

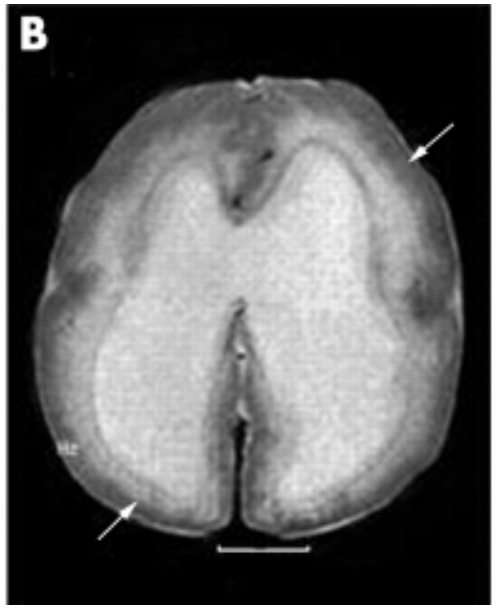


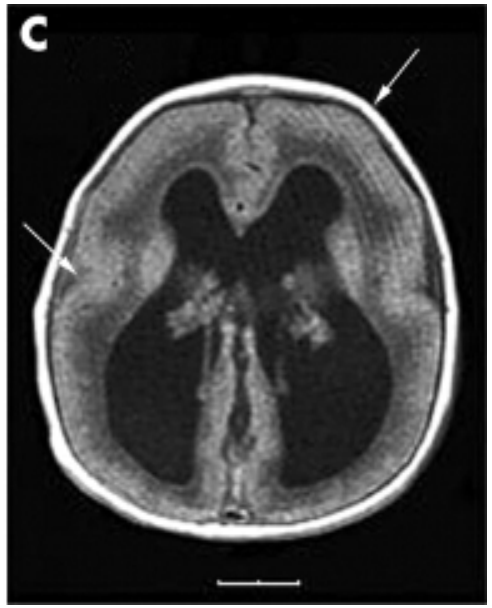
Abnormalities in the corpus callosum may occur in SmithLemli-Opitz syndrome

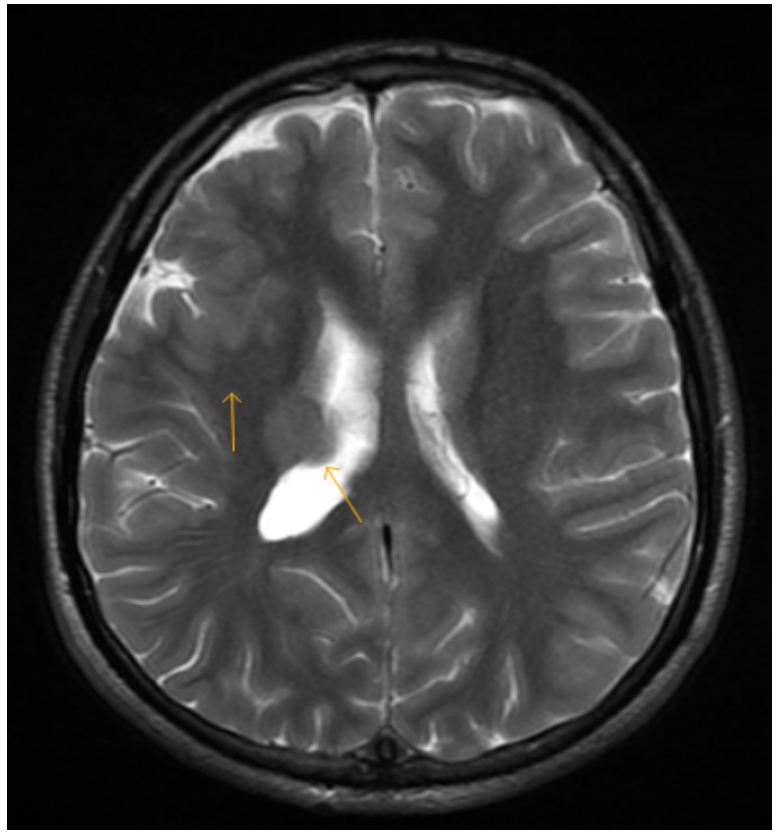


- heterotopias and other structural brain abnormalities may be seen in congenital muscular dystrophy









- Deep white matter changes can be seen in Lowe syndrome, a peroxisomal defect.

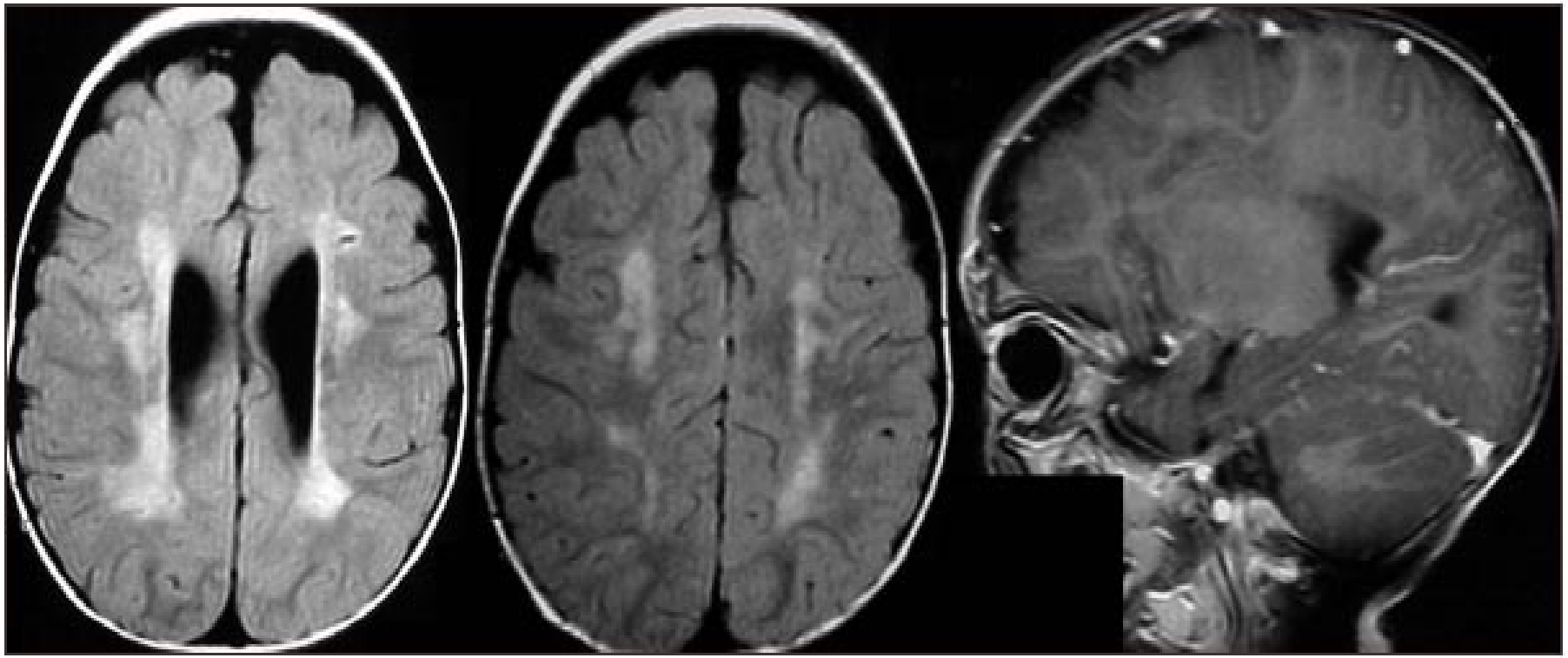


Fig 1. MRI examination at 21 months of age. Axial FLAIR (fluid-attenuated inversion recovery) and sagital T1-weighted post gadolinium (MR contrast agent). T2 weighted images show white matter hyperintensities in the periventricular and centrum semiovale regions.

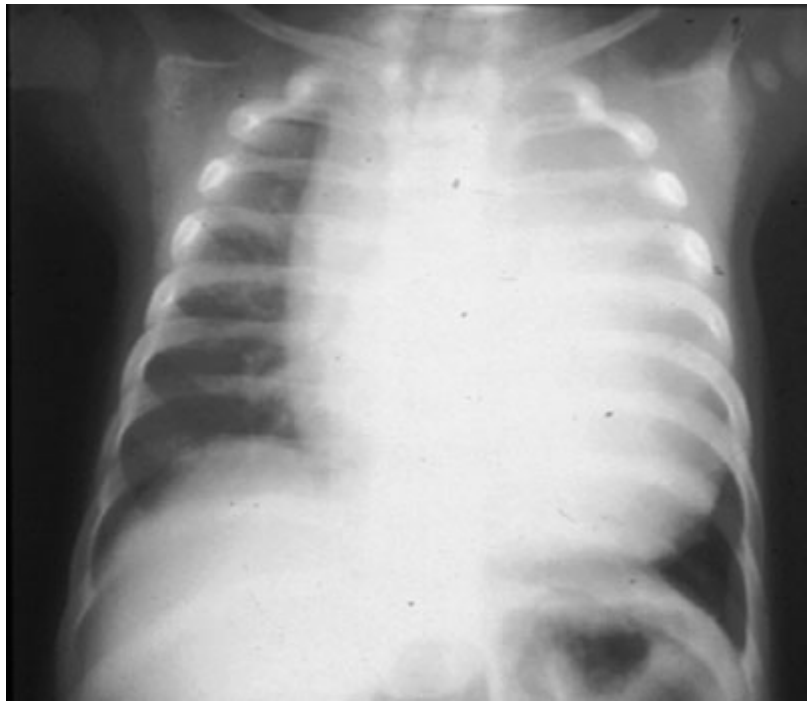
- We have to put all the finding together to reach the possible diagnosis

CASE :

- six month old male infant, found to be hypotonic, weak, delayed milestones and large tongue
- Family history were free except for unexplained death of his cousin at the age of 2 years, and the parents are far relatives.
- Basic lab investigations were normal , CXR : big heart !!
- WHAT DO YOU THINK !!!! What investigation do you like to do next !!

- Could be ? Pompe disease or acid maltase deficiency …
- Inherited in an autosomal recessive pattern.
- Caused by a deficiency in the lysosomal enzyme acid alpha glucosidase, present in all tissues.
- Absent enzyme activity in the infantile form results in abnormal glycogen deposition in the skeletal, cardiac, and smooth muscles, leading to hypertrophic cardiomyopathy, feeding abnormalities, hypotonia, weakness, respiratory insufficiency, and ultimately, death.
- Hypotonia is the result of glycogen storage in the brain, spinal cord, and muscle, producing a mixed central and peripheral clinical picture

- Cardiomegaly almost always is diagnostic.
- Most patients die of cardiac failure by 12 months of age.
- The diagnosis is established by muscle biopsy, with a definitive diagnosis being demonstrated by deficient acid maltase activity in fibroblasts or other tissues



- Early diagnosis results in early institution of enzyme replacement therapy, which minimizes morbidity and prolongs survival

CASE

- 3 month old infant, was healthy with a free pre and perinatal history.
- Presented by his father with a history of sudden onset of weakness, lethargy, loss of head control and weak cry for the last 4 days
- On examination found to have : ptosis, sluggish pupillary response to light, ophthalmoplegia, poor suck, decreased gag reflex, and an expressionless face , hypotonia, weakness and absent DTR !!!
- Free family history.
- Social history, parents are divorced and he his living with his father and grandmother in a village
- WHAT DO YOU THINK !!

- DDX : sepsis, intoxication, electrolyte imbalance, encephalitis, myasthenia gravis, and polyneuropathies ….
- Presentation of an acute episode of hypotonia !
- his grandma said that he had constipation and she fed him some honey !!
- SO !!!

- Infantile botulism :

- Human botulism ordinarily results from eating foods contaminated by preformed exotoxin of the organism Clostridium botulinum.

- The exotoxin blocks the release of acetylcholine at the neuromuscular junction, which results in cholinergic blockade of skeletal muscle and end organs innervated by autonomic nerves.

- infants afflicted with botulism are between 2 and 26 weeks of age

- A prodrome of constipation, lethargy, and poor feeding is followed in 4 to 5 days by progressive bulbar and skeletal muscle weakness and loss of DTRs, Progressive muscle paralysis can lead to respiratory failure.

- Spinal muscular atrophy type I and metabolic disorders can mimic infantile botulism.
- Patients who have spinal muscular atrophy type I generally have a longer history of generalized weakness, do not typically have ophthalmoplegia, and have normal anal sphincter tone.
- Dx : detecting botulism toxins or spores in stool is the best way to confirm the diagnosis.

Treatment :

- intravenous human botulism immuneglobulin, which neutralizes all circulating botulinum toxin, and supportive therapy for airway maintenance, ventilation, and nutrition.

- Infantile botulism usually is a self-limited disease lasting 2 to 6 weeks, and recovery generally is complete, although relapse can occur in up to 5% of infants.

CASE :

- Seven month old female patient, pre and perinatal hx was free, presented by his mother that he cant support his head and can't set even with support.
- She started to smile recently and cant reach for objects yet but she transfer between hands.
- On examination, he is not dysmorphic, growth parameters between 50 % and 75 % with hypotonia, generalized symmetric flaccidity of muscles and hyper mobile joints.
- Family history was free, and all labs and images were normal.

- On follow up at the age of 19 months, his tone was slightly improving, with abdominal protrusion, flat feet, walking on tip-toe, his vocabulary was only 3 words without meaning, and he doesn't have mature pincer grasp !

- What do you think !!!!

- Benign congenital hypotonia !!

- This nonprogressive neuromuscular disorder presents at birth with delays in achieving developmental milestones. Improves with the maturity of the central nervous system.

- This is a diagnosis of exclusion,the history must not suggest any neurologic or metabolic disorders.

- Patients must be counseled about the possibility of joint dislocations in the future. An increased incidence of intellectual disability, learning disability,or other sequelae of cerebral abnormality often is evident later in life, despite the recovery of normal muscle tone

CASE:

- A five-month-old infant girl, her family noticed that she is unable to raise her upper body when lying prone. She often squealed and seemed to respond to her name. No loss of milestones was reported.
- Pre and perinatal history was free.
- Admitted twice before due to chest infection.
- family history was unremarkable and there was no consanguinity.

- On examination, the infant looked well, with no dys-morphic features, She had a strong cry and no fasciculations of the tongue were noted, She had marked hypotonia, weak grasp and abscent DTRs

- All labs including creatine kinase were normal, brain imaging normal
- EMG confirmed dysfunction in the anterior horn cells,
- Dx : Werdnig-Hoffman disease or SMA I
- Diagnosis confirmed by genetic study (SMN gene)

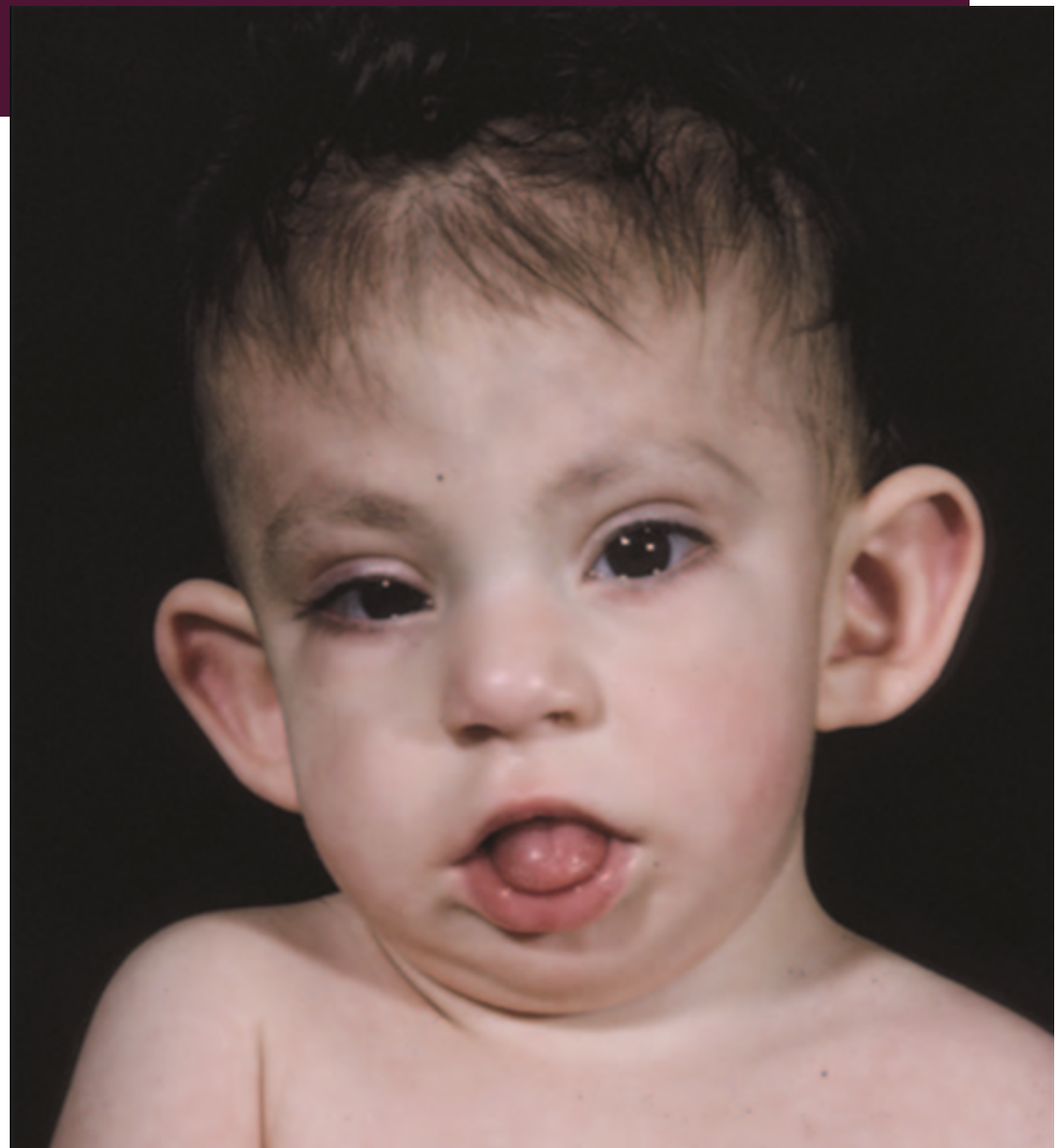
- SMAs are a group of diseases characterized by a progressive loss of spinal anterior horn cells, leading to muscular denervation, atrophy and weakness.
- The most common forms of SMA are transmitted by autosomal recessive inheritance, with the gene defect localized to the motor neuron survival gene (SMN gene) on chromosome 5q.
- feeding and swallowing are compromised, and death usually results from aspiration and respiratory insufficiency.

- Treatment of SMA type 1 is supportive.

CASE

- 15 month old male patient, presented by his mother that he cant walk yet and he says no words

- Pre and perinatal hx free
- Family history free
- On Examination found to have dysmorphic features, normal power and reflexes



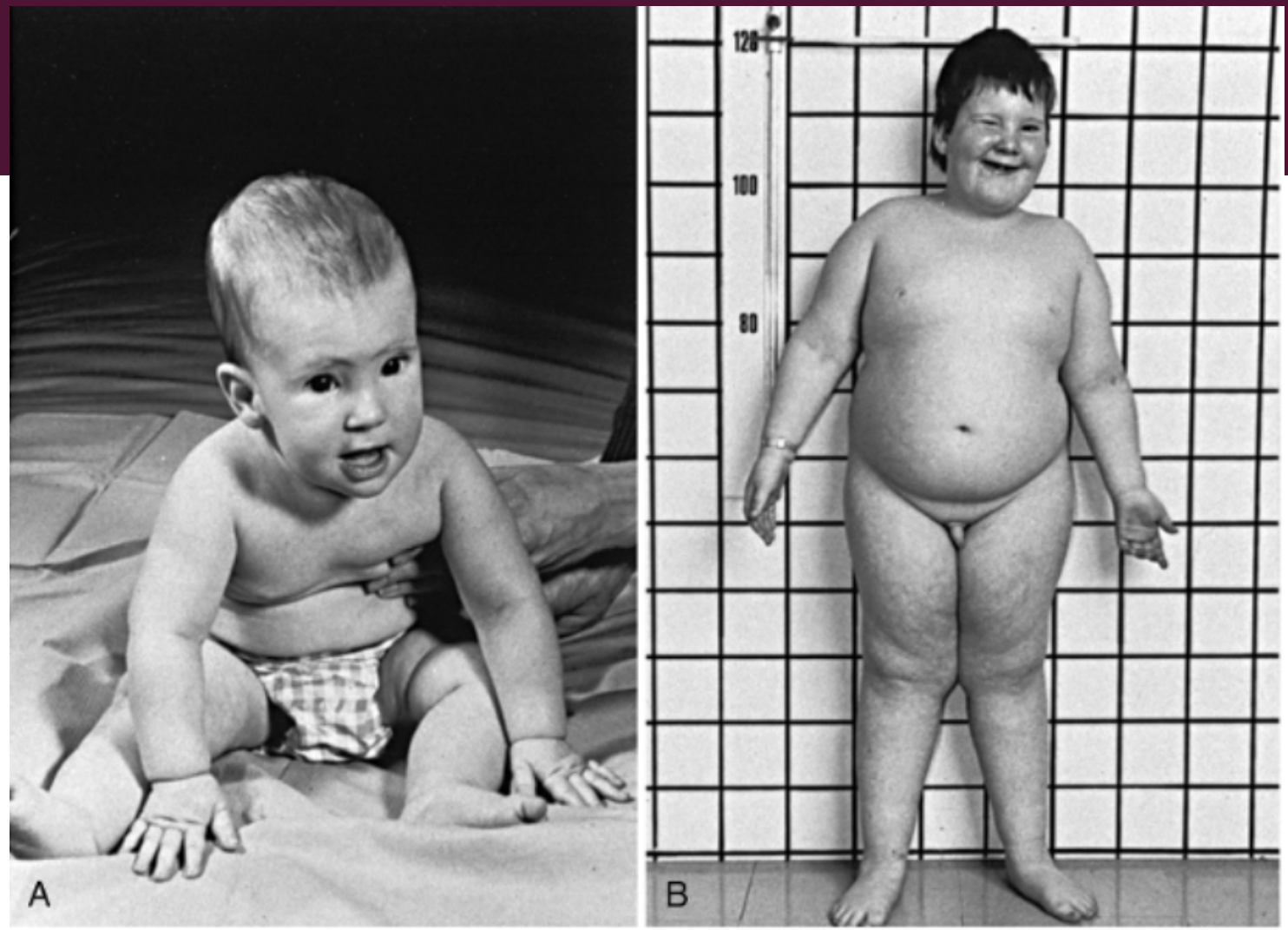
- Kabuki syndrome is a multiple congenital anomaly syndrome associated with hypotonia and feeding problems and is characterized by specific facial features.

- mild-to-moderate intellectual disability, postnatal growth delay, skeletal abnormalities, and unusual dermatoglyphic patterns that have prominent finger tip pads

- Physical features include long palpebral fissures with eversion of the lateral lower eyelid, large protuberant ears, cleft palate, tooth abnormalities, skeletal abnormalities, and cardiac and renal defects.

- Kabuki syndrome is caused by mutations in the KMT2D gene or the KDM6A gene. And inherited in an autosomal dominant pattern if they have the gene

- Fragile X syndrome : (4 %) : characterized by mild-to-profound intellectual disability, poor eye contact, autistic features, macrocephaly, large ears, epicanthal folds, a thickened nasal bridge, and increased testicular size in puberty, expansion of a trinucleotide repeat (CGG) in the promoter region of the FMR1 gene at Xq27.3
- Affected individuals have more than 200 .
- hypotonia generally is a feature during infancy, it is mild, and most children who have fragile X syndrome are not diagnosed early in life until a delay in developmental milestones is detected.


A
B
120
100
80

- Prader-Willi syndrome (5 %) is characterized by hypotonia, hypogonadism, intellectual disability, short stature, and obesity. Affected patients present at birth with profound hypotonia and feeding problems until 8 to 11 months of age, when they develop low-normal muscle tone and insatiable appetites.

- Prominent physical features during childhood include a narrow bifrontal diameter, strabismus, almond-shaped eyes, enamel hypoplasia, and small hands and feet

- 75% of patients is a deletion of the long arm of chromosome 15 at q11-q13.
- In all cases studied, the paternally derived chromosome has been deleted.
- Maternal uniparental disomy accounts for an additional 20% of cases.
- The remaining 5% are due to a mutation of the imprinting center or to a chromosomal translocation

THANK YOU