Floppy Child: Clinical approach

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Objectives:

- Definition of hypotonia
- Key elements in History and Clinical examination for child with floppiness
- How to investigate for hypotonia
- Overview of common neurological disorders with hypotonia

Definition

- The floppy infant syndrome is refers to an infant with generalized hypotonia presenting at birth or in early life.
- Characterized by poor muscle tone results in an inability to maintain normal posture during movement and rest
- Hypotonia divided to :

➢ Central

➢ Peripheral

➢ Mixed or combined

History : Key elements :

- Prenatal, neonatal and perinatal assessment:
  - Fetal movements
  - Breech presentation
  - Polyhydramnios or oligohydramnios
  - Congenital infection
  - Details of perinatal birth
  - Preterm delivery
  - Birth anoxia, delivery complications, low APGAR scores

Prenatal, neonatal and perinatal assessment:

- Ventilator assistance soon after birth
- Feeding difficulties, weak sucking, NGT feeding
- Neonatal seizures or apnea
- Encephalopathic state

History : Key elements :

- A history of hip subluxation or arthrogryposis increases the likelihood of hypotonia in utero
- A developmental assessment
- Motor delay with normal social and language development decreases the likelihood of brain pathology
- A dietary/feeding history may point to diseases of the neuromuscular junction
- Difficulty with swallowing
- Loss of milestones → Neurodegenerative disease

History : Key elements :

- Family history:
  - ➢History of repeated abortions
  - ➢Premature death (metabolic or muscle disease)

- History of honey or corn syrup consumption; contamination of these products with Clostridium botulism → Infantile botulism

Physical examination:

- Consciousness, alertness and higher mental
- Posture: full abduction and external rotation of the legs as well as a flaccid extension of the arms

Physical examination:

Dysmorphic features: Increase the likelihood of CNS dysfunction

Ptosis and extraocular muscle weakness

The quality of the cry :

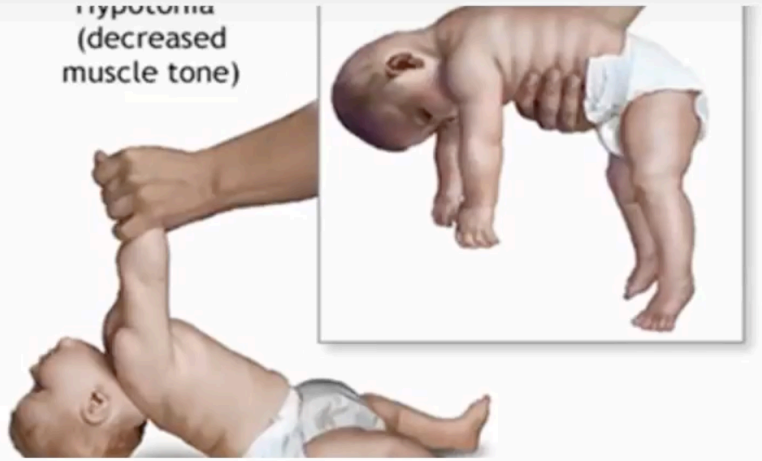
A high-pitched or unusual-sounding cry ------- CNS pathology

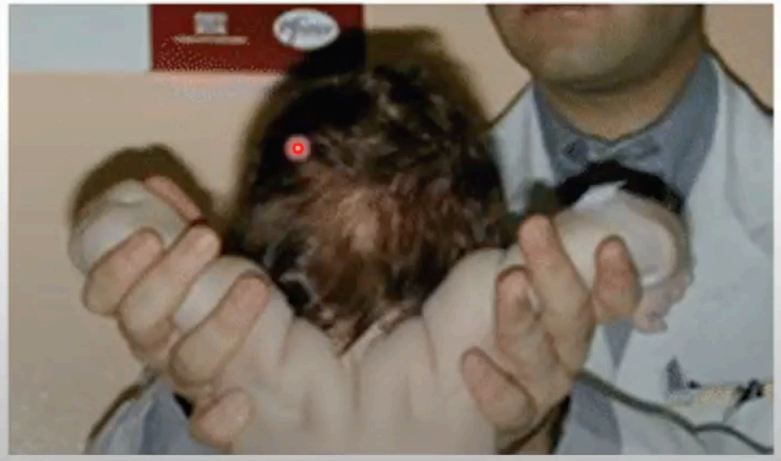
A weak cry may reflect --------- diaphragmatic weakness

A fatigable cry may suggest ------- a congenital myasthenic syndrome

Physical examination:

- While assessing the tone, Child should be alert, not crying
- Truncal and nuchal tone may be best examined using tests of horizontal and vertical suspension





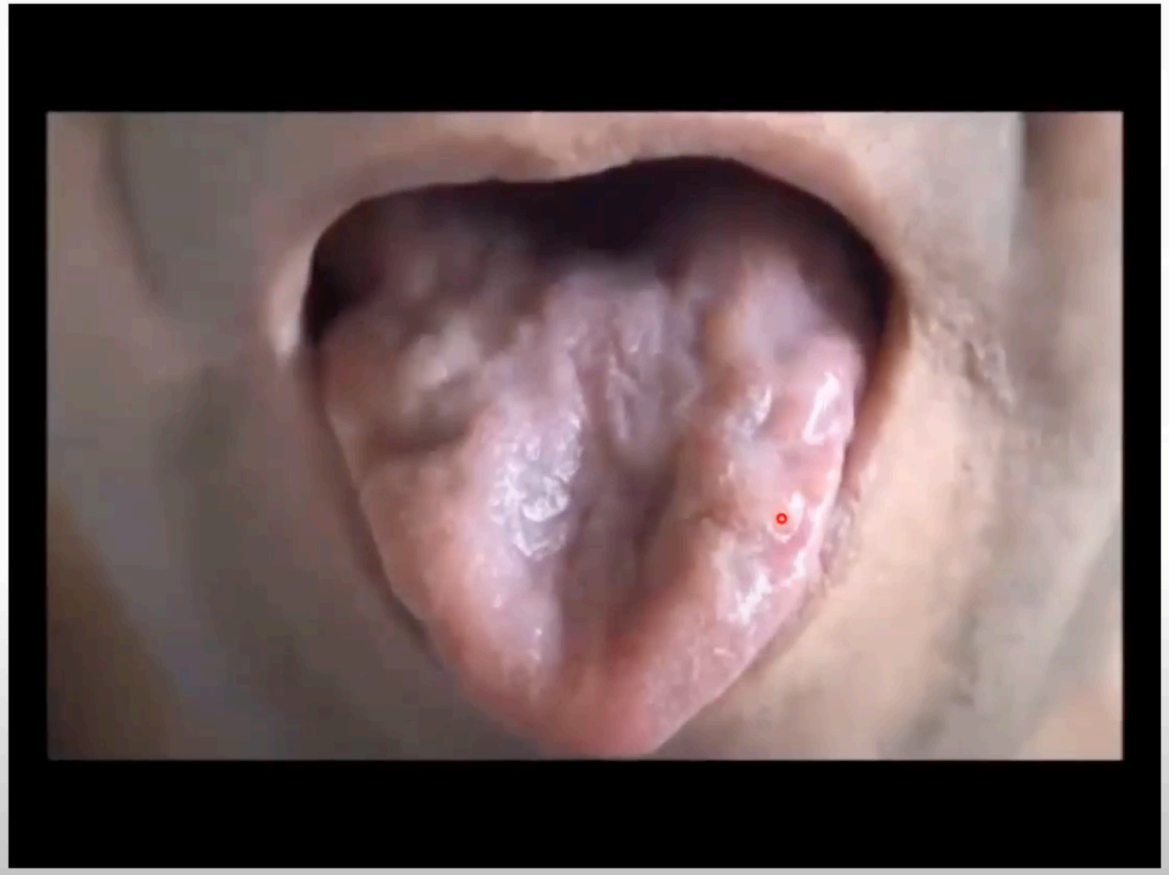
Physical examination:

A head-to-toe physical examination is required to assess for potentially associated organ dysfunction

A myopathic face, which is a long, flat, expressionless face associated with tented upper lip (fish mouth) and sometimes high-arched palate

Examination of fundi is needed to exclude optic atrophy (demyelinating disorders) and retinal changes(metabolic or congenital infections)

Tongue fasciculation :



Toungue Fasciculation:

Physical examination:

- Weight, length, and head circumference should be measured and plotted on percentile charts
- Power:
  - Weak V Strong
  - Proximal weakness : Myopathic except Myotonic dystrophy
  - Distal weakness: Neurogenic except SMA

Physical examination:

- DTR:
  - Hyperreflexia
  - Hypo/Areflexia
- Examination of the back is critical in children with paraplegia to exclude spina bifida

Physical examination:

- Heart : R/O associated metabolic diseases
- Abdomen: Organomegaly → Lysosomal or storage diseases
- Renal : Renal failure → Lowe syndrome
- Parents examination:

➢ Transitory neonatal myasthenia

➢ Congenital myotonic dystrophy

Investigations:

- The history and physical examination should guide the investigations
- Paralytic hypotonia with significant weakness and without cognitive delay suggests a peripheral neuromuscular problem
- Non-paralytic hypotonia without significant weakness can be attributed to a central cause which may be neurological, genetic or metabolic

Floppy strong

- Increased tendon reflexes
- Extensor plantar response
- Sustained ankle clonus
- Global developmental delay
- Microcephaly or suboptimal head growth
- Convulsions
- Axial weakness
- Upper motor neuron disorder
- Central hypotonia

Floppy weak

- Hypo- to areflexia
- Selective motor delay
- Normal head circumference and growth
- Preserved social interaction
- Weakness of antigravitational limb muscles
- Low pitched weak cry
- Tongue fasciculations
- Paradoxical chest wall Movement
- Lower motor neuron disorder
- Peripheral hypotonia

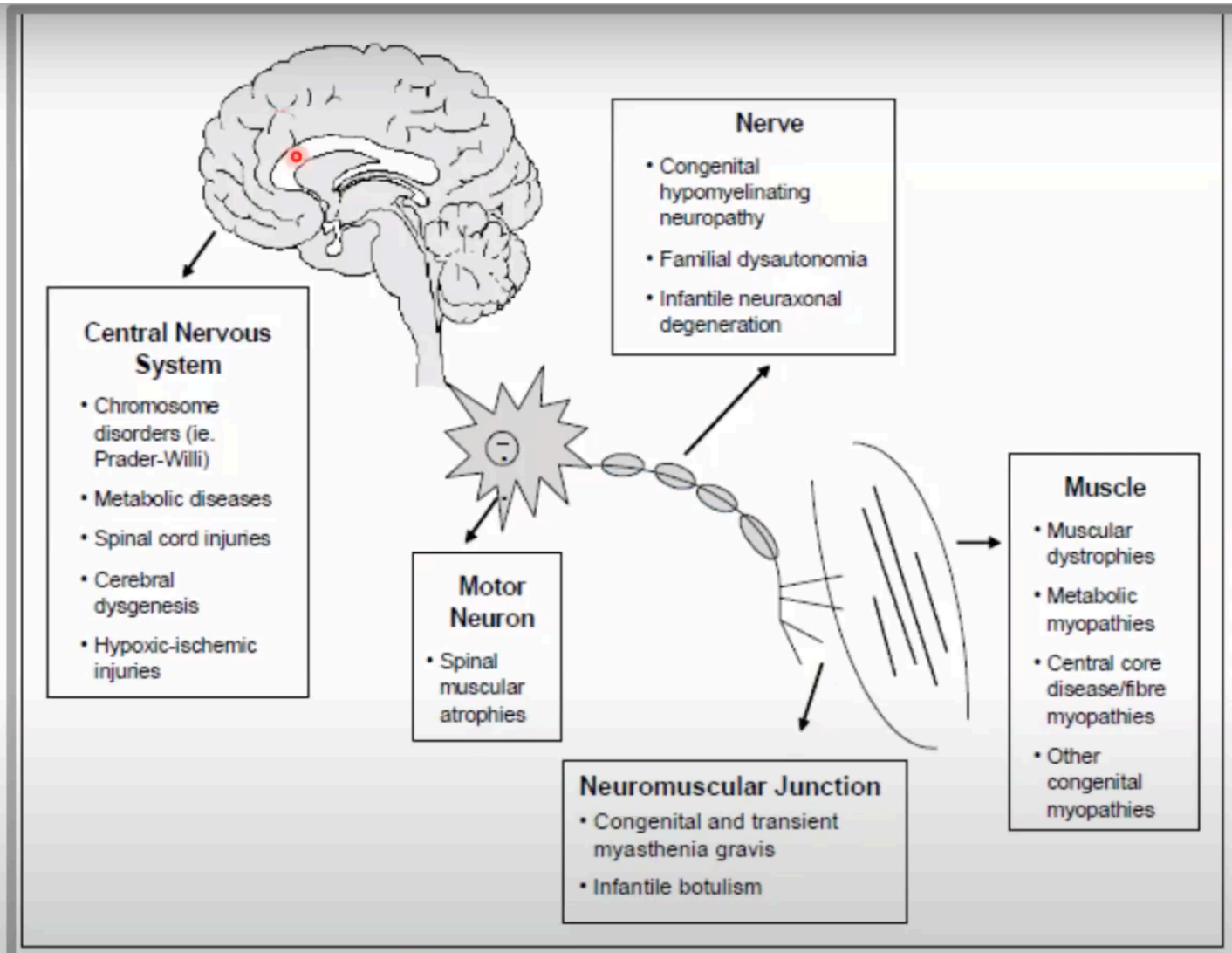


Figure 1) *Anatomical-clinical correlation illustrating differential diagnosis of hypotonia in infancy*

Pattern of weakness and localization in the floppy infant

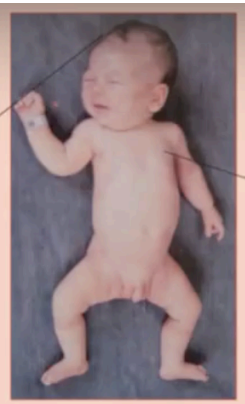
Anatomical region of hypotonia	Corresponding disorders	Pattern of weakness and involvement
Central nervous system	Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma	Central hypotonia Axial hypotonia more prominent Hyperactive reflexes
Motor neuron	SMA	Generalized weakness, often spares the diaphragm, facial muscles, pelvis and sphincters
Nerve	Peripheral neuropathies	Distal muscle groups involved Weakness with wasting
Neuromuscular junction	Myasthenia syndromes Infantile botulism	Bulbar, oculomotor muscles exhibit greater degree of involvement
Muscle	Congenital myopathies Metabolic myopathies CMD Congenital myotonic dystrophy	Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures

Investigations:

- **General Investigations:** TSH, free T4, electrolytes (including calcium)
- **CNS Dysfunction Suspected:** CT/MRI head, consider EEG, consult neurology, and consider karyotype
- **Metabolic Disease Suspected:** Urine and serum amino acids, urine organic acids,blood gas, serum ammonia, liver function tests
- **Lower Motor Neuron Disease Suspected:** Creatine kinase, electromyography (EMG), nerve conduction studies and muscle biopsy may be considered

Investigations:

- **Genetic testing**



Floppy strong

Increased tendon reflexes
Extensor plantar response
Sustained ankle clonus
Global developmental delay
Microcephaly or suboptimal head growth
Obtundation convulsions
Axial weakness a significant feature

Floppy weak

Hypo- to areflexia
Selective motor delay
Normal head circumference and growth
Preserved social interaction
Weakness of antigravitational limb muscles
Low pitched weak cry
Tongue fasciculations
Paradoxical chest wall movement

Upper motor neuron disorder
Central hypotonia

Lower motor neuron disorder
Peripheral hypotonia

Creatine kinase assay
EMG
Nerve conduction studies

Genetic studies
Karotyping
FISH methylation studies
VLCFA

CT/MRI

DNA-based mutation analysis if available

Muscle or nerve biopsy

Triosomy 21
Prader-Willi syndrome
Zellweger syndrome

Hypoxic ischaemic encephalopathy
Cerabral malformations

Spinal muscuar dystrophy
Congenital myotonic dystrophy
Congenital muscular dystrophies

Congenital structural myopathies

History:

Prenatal History: *TORCH infections? Drugs or alcohol? Maternal illness?* Fetal movements?
Neonatal History: Delivery complications? *Preterm delivery? Seizures?* Initial presentation of hypotonia?
Past Medical History: History of presenting symptoms? Associated symptoms? Symptoms of systemic disease? Rate of symptom progression?
Developmental History: *Delayed milestone attainment? Loss of milestones?* Motor, social and language incongruence?
Feeding History: Stamina with feeding? Choking or aspiration? Constipation? Honey or corn syrup?
Family History: Other children? Consanguinity? *Developmental delay?* Neurological disease? Premature death? *Metabolic or genetic diseases?*

General Physical Examination:

Head and neck: *Microcephaly? Dysmorphic features?* Ptosis? Facial expression? Nutritional wasting?
Systems: *Cardiovascular findings? Liver enlargement? Splenomegaly? Skeletal abnormalities?* Arthrogryposis?

Neurological Examination:

Objective – Localize the lesion.

Cranial nerves: Extraocular movements? Muscles of facial expression? Fasciculations of tongue?
Tone: Posture? Horizontal and vertical suspension? *Scissoring or spasticity?*
Strength: Proximal versus distal weakness? Symmetry?
Reflexes: *Hyperactive?* Symmetry? Readily elicited? *Clonus?*
Muscles: Atrophy? Symmetry?

	Motor Neuron	Nerve	NM Junction	Muscle
Tone*	↓	↓	normal/↓	↓
Strength	↓	↓	normal/↓	↓
Reflexes	absent	absent	normal/↓	absent/↓
Muscle Atrophy	↓	↓	normal/↓	normal/↓

Investigations:

General Investigations: TSH, free T4, electrolytes (including calcium)
CNS Dysfunction Suspected: CT/MRI head, consider EEG, consult neurology, and consider karyotype
Metabolic Disease Suspected: Urine and serum amino acids, urine organic acids, blood gas, serum ammonia, liver function tests
Lower Motor Neuron Disease Suspected: Creatine kinase, referral to neurology for specialized tests

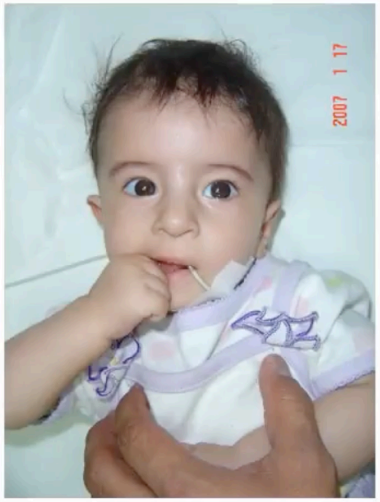
Management:

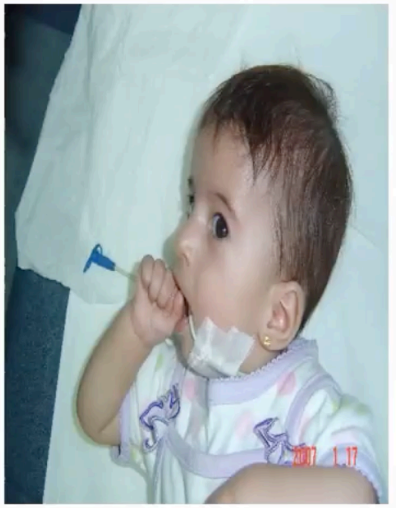
- Treatment is directed towards the underlying etiology, clinical manifestations or complications of the disease
- Supportive therapy
- Physiotherapy and Occupational therapy

Case 1:

Five month old girl presented with:

- Poor feeding since birth
- Respiratory distress,Recurrent chest infection
- NGT feeding
- hypotonia ,absent ankle reflexes





Investigations

- CBC, Renal, Hepatic profile : Normal
- CK 39
- Chromosome Analysis: 46xx
- NCS,EMG : Normal
- SMN gene for SMA : Negative

Investigations

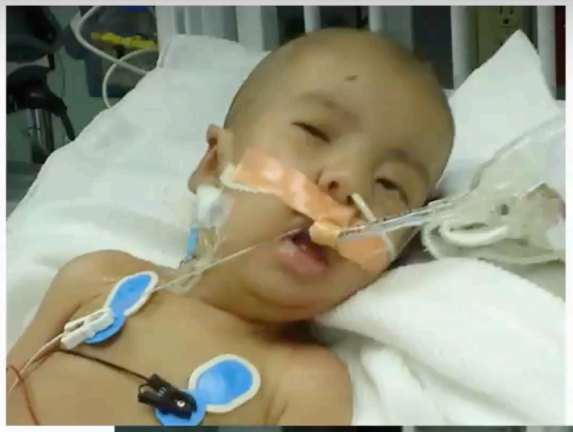
FISH study :

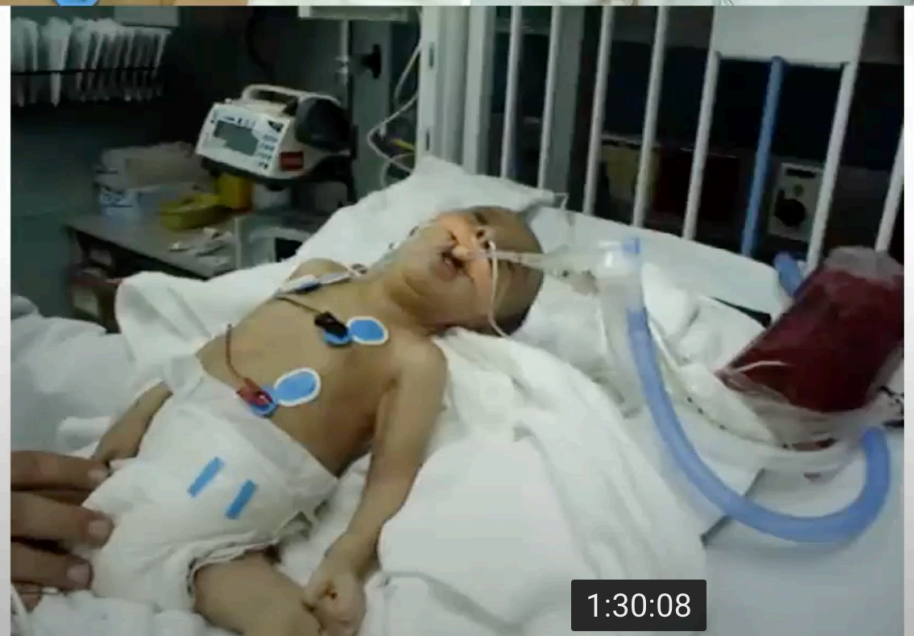
Deletion within 15q11.2

Diagnosis: Prader-Willi Syndrome(PWS)

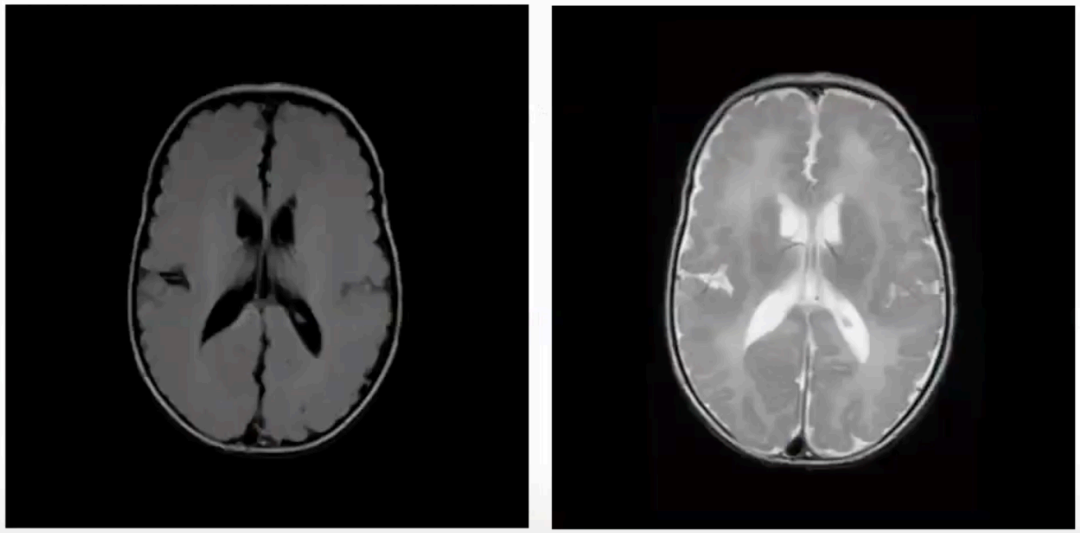
Case 2:

- Newborn FT,SVD
- NICU admission due to poor sucking and hypotonia
- At age of 4 days had convulsion.
- Hypoglycemia : adrenal insufieciency



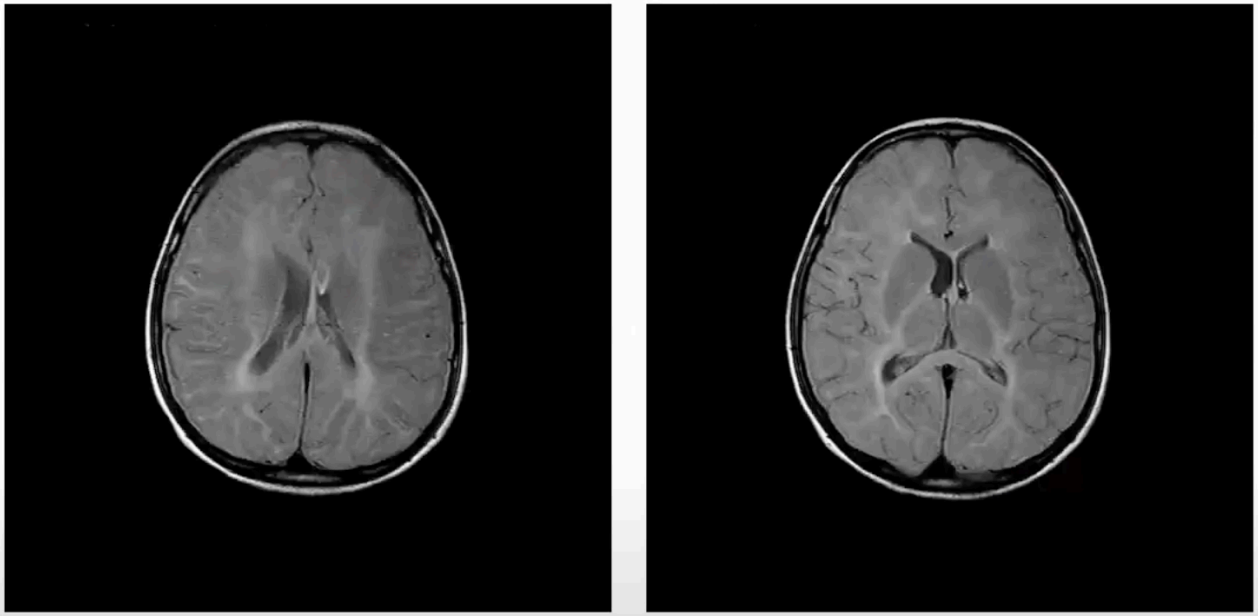


- MRI brain : Polymicrogyria
- VLCFA: High
- Genetic testing : PEX13
- Diagnosis: Peroxisomal disorder (Zellweger syndrome)



Case 3:

- A 7-year old girl
- Pendular nystagmus
- Failure to thrive
- Developmental delay
- No seizure

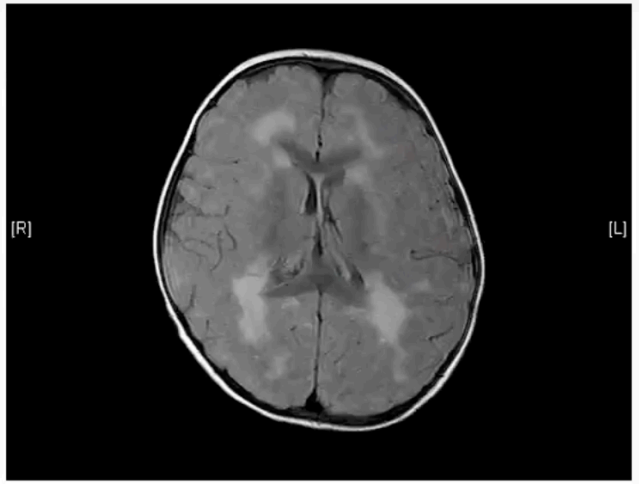


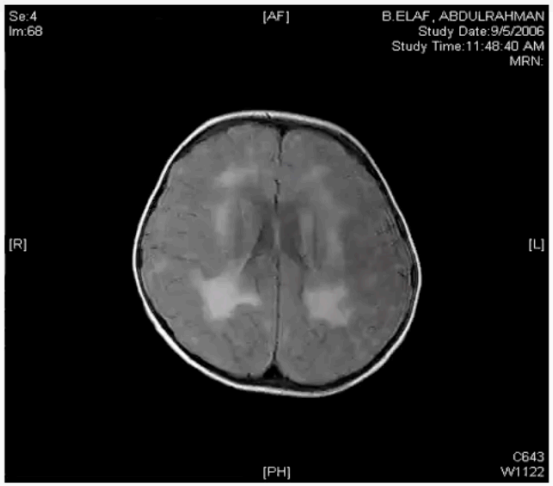
- Genetic testing : homozygous mutation detected on the GJC2
- Diagnosis: Pelizaeus-Merzbacher-like disease (PMLD)

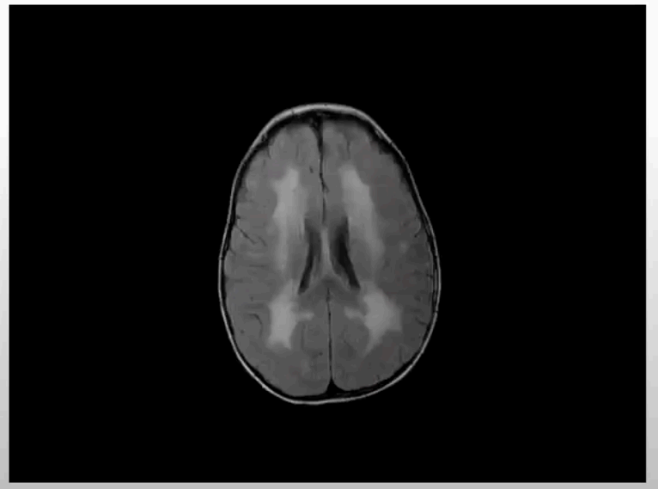
Case 4:

2.5 year old girl with

- Developmental delayed (motor)
- Recurrent choking spells
- Recurrent chest infections
- Hypotonia with absent DTR
- CK 2000







- MEROSIN LAMA2 GENE: Positive

- Diagnosis: MEROSINE-DEFICIENT CONGENITAL MUSCULAR DYSTROPHY (MDCMD)

Case 5:

- 5-months old girl referred with motor delay , can't roll over, can't control head. Normal vision and hearing . Socially laughing, interactive with surrounding.
- Had one admission with chest infection at age of 3 months
- Pregnancy and birth:Unremarkable
- On examination: Conscious , No tongue fasciculation , CN: Normal. EOM: Full.
- Marked hypotonia on horizontal and vertical suspension. Tightness of the hip adductors and knee extensors was noted
- DTR: Not elicited
- CK : Normal

Case 5:

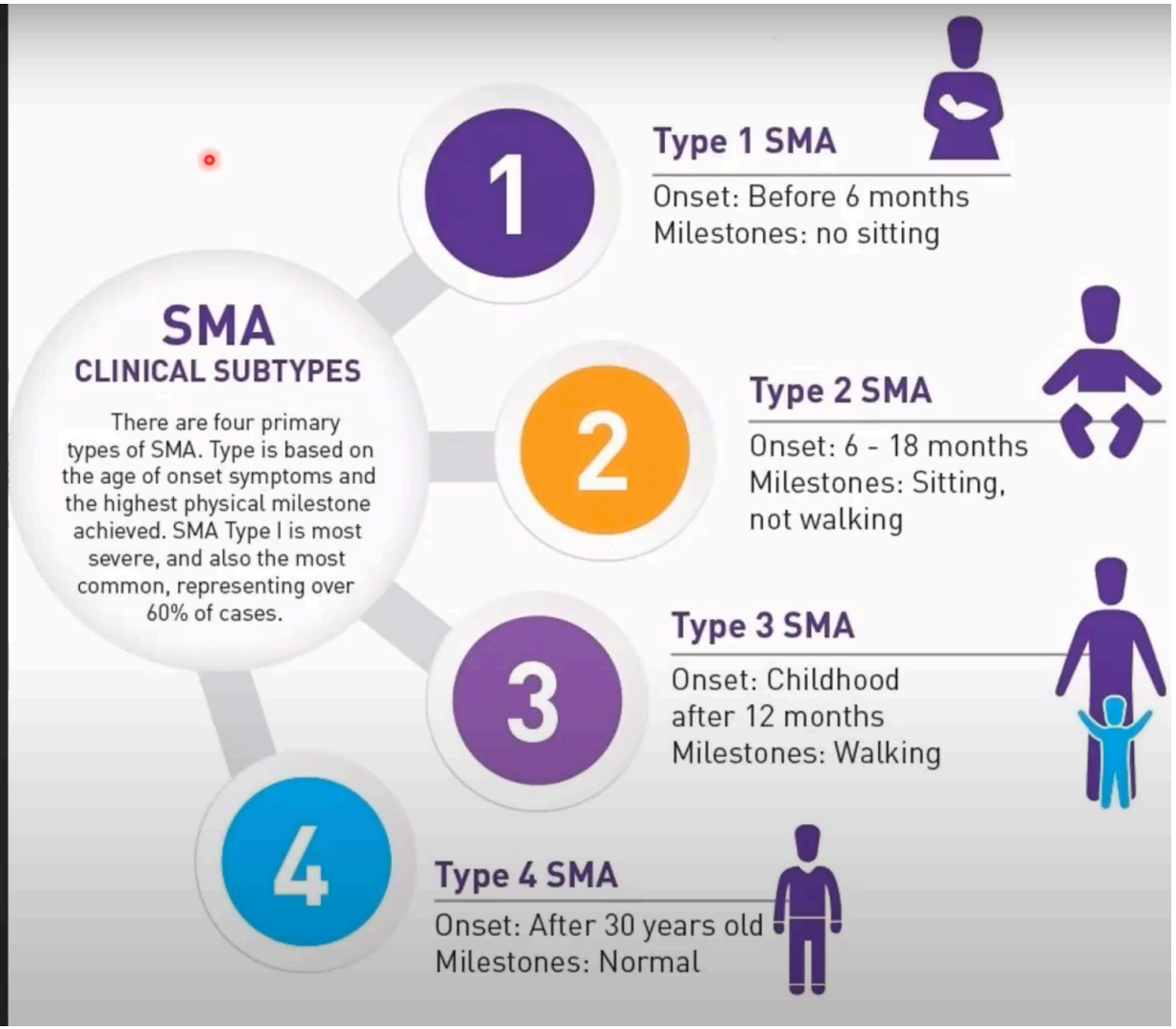
- Genetic Testing confirmed the diagnosis of :

SMA type I

SMA

- An autosomal recessive disorder
- degeneration of the anterior horn cells, leading to progressive weakness and wasting of skeletal muscles
- Due to mutations in the survival motor neurone (SMN) gene.
- This is the second most common cause of neuromuscular disease in after Duchenne muscular dystrophy.

SMA types


SMA
CLINICAL SUBTYPES
There are four primary types of SMA. Type is based on the age of onset symptoms and the highest physical milestone achieved. SMA Type I is most severe, and also the most common, representing over 60% of cases.
1
Type 1 SMA
Onset: Before 6 months
Milestones: no sitting
2
Type 2 SMA
Onset: 6 - 18 months
Milestones: Sitting, not walking
3
Type 3 SMA
Onset: Childhood after 12 months
Milestones: Walking
4
Type 4 SMA
Onset: After 30 years old
Milestones: Normal

Treatment

- Standard of care : Rehabilitation and supportive care
- Medications :

Case6:

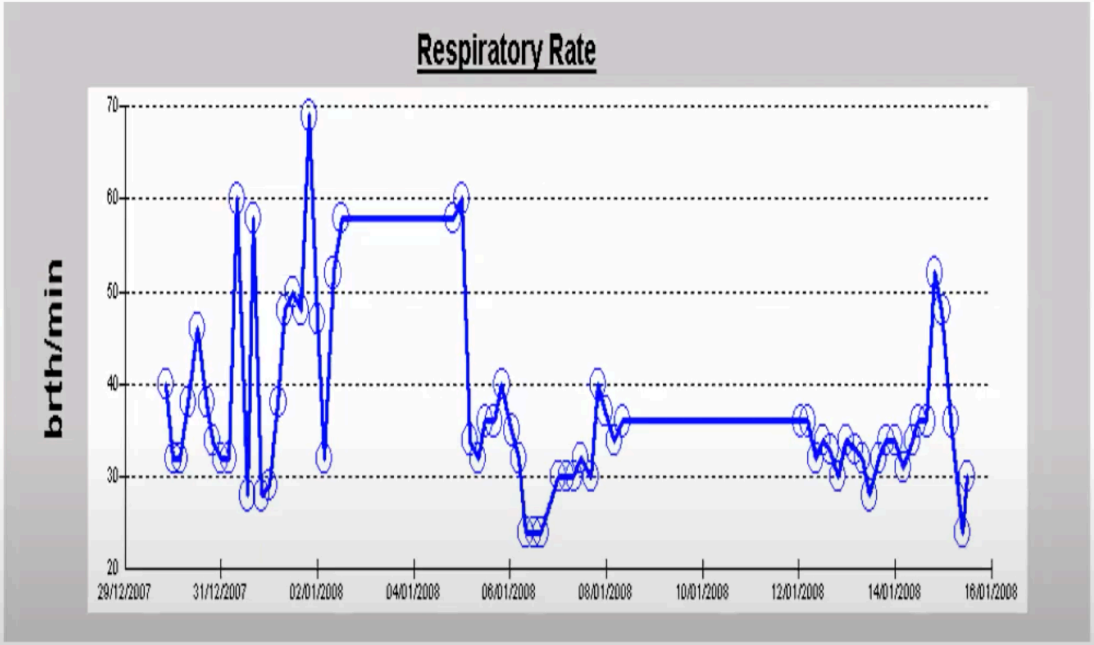
- 7 months old Saudi boy.
- FT, NSVD.
- Developed tachypenia which required admission to NICU for 11 days.
- At 4 months, admitted with chest infection.

Case6:
Developmental History

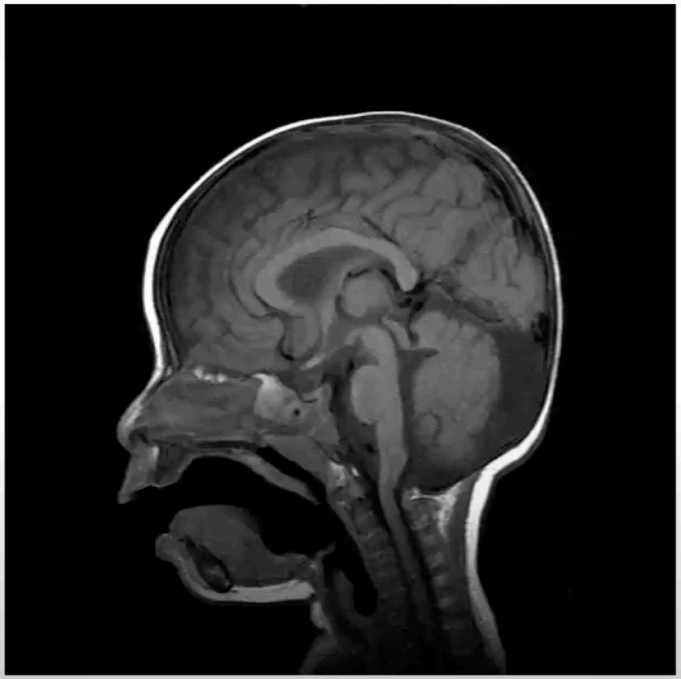
- Can’t control his head
- Can’t sit even with support
- Can’t reach for an object
- Can’t fix and follow
- Can hear

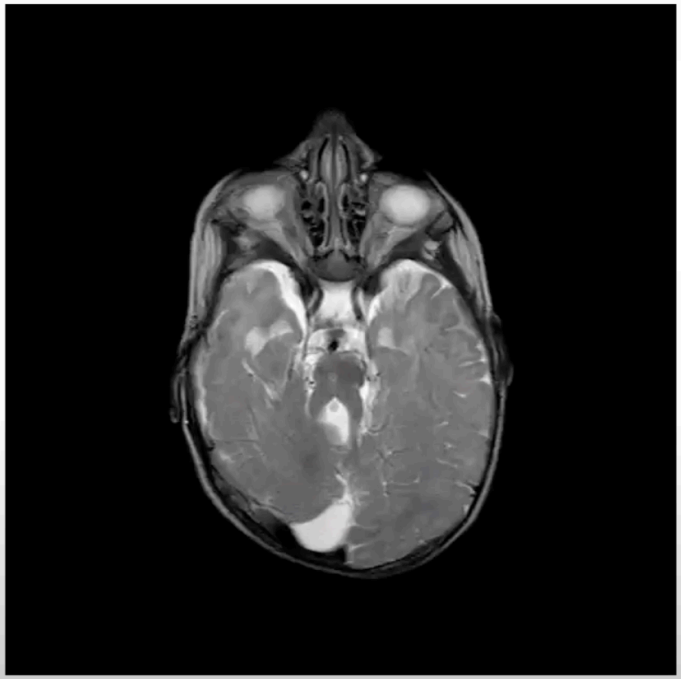
Case6:

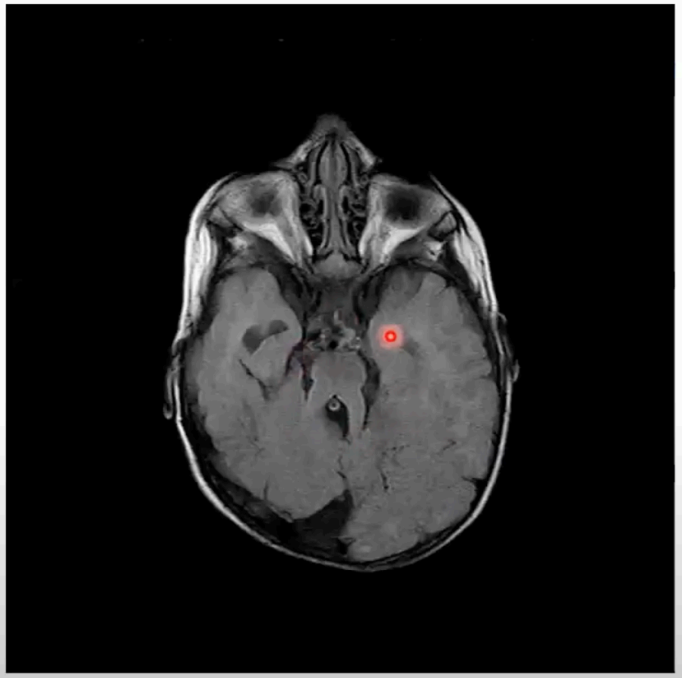
- Looks well, active, tachypneic
- No dysmorphic features
- Hypotonic.
- Moving all limbs symmetrically against gravity.
- DTR + 3 .



Case6:







Diagnosis

- Joubert Syndrome

Case7:

- 8- year-old girl referred due to bilateral ptosis noticed since birth
- Diurnal variation
- History of difficulty in walking especially by the end of the day
- History of weak swallowing and recurrent chest infection
- Examination showed hypotonia
- Proximal muscle weakness
- DTR: +1

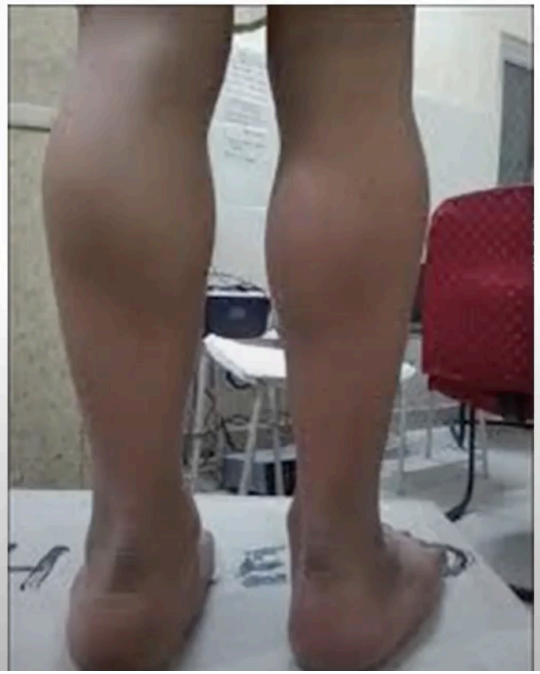
Case7:

- Genetic testing :
- Mutations in the acetylcholinesterase (AChE) collagen-like tail subunit gene (*COLQ)*
- Diagnosis: Congenital Myasthenia

Case 8:

- 4-year-old boy presented with
- Difficulties in jumping and climbing stairs
- Mild speech delay
- CK: 14000

Exam showed this sign:

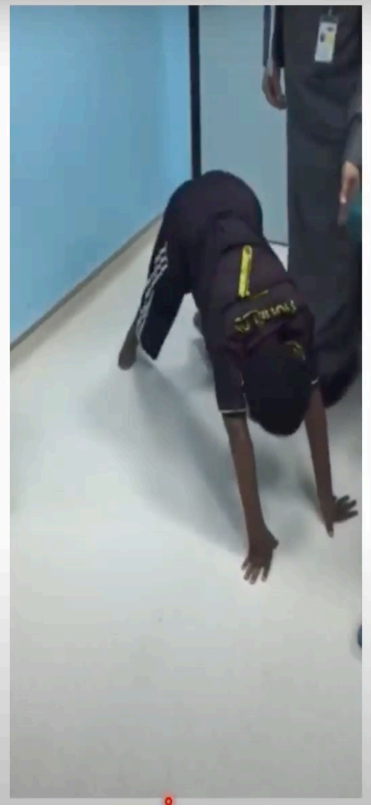


Duchenne muscular dystrophy

- DMD is the most common neuromuscular disorder
- Affecting 1 in 4000 male infants.
- It is inherited as an X-linked recessive disorder, although about a third have new mutations.
- It results from a deletion on the short arm of the X chromosome (at the Xp21 site). This site codes for a protein called dystrophin

DMD

- Children present with a waddling gait and/or language delay
- Difficulties in climbing stairs , run slowly compared to their peers.
- Average age of diagnosis 4 - 5.5 years
- They will show Gowers's sign (the need to turn prone to rise).
- There is pseudohypertrophy of the calves because of replacement of muscle fibres by fat and fibrous tissue



Treatments

- Supportive and rehabilitation
- Cardiac assessment
- Medications: steroid

Treatments: for a certain genetic mutation

- Eteplirsen (Exondys 51)
- Golodirsen (Vyondys 53)
- Ataluren

Mutation-specific Exon-skipping & Read-through Therapies

Company	Name	Target DMD patients	Current Phase	Primary Endpoint	Expected results
Nonsense mutations Read-through					
PTC	Translarna	*13%*	M (ex-US) / 3 (US)	6MWT	1Q 2020
PTC	Translarna	*13%*	M (ex-US) / 3 (US)	Dystrophin Level	4Q 2019
Exon 51					
Sarepta	Exondys 51	*13%*	M (US)	6MWT	2Q 2019
Sarepta	SRP-5051	*13%*	1		3Q 2019
Wave	WVE-210201	*13%*	1		2H 2019
Daiichi	DS-5141	*13%*	1/2		Apr-18
Exon 53					
Sarepta	Golodirsen	*8%*	F	6MWT	2022
Sarepta	SRP-5053	*8%*	PC		
Wave	WVE-N531	*8%*	PC		2H 2020
Exon 45					
Sarepta	Casimersen	*8%*	3	6MWT	2022
Sarepta	SRP-5045	*8%*	PC		
Wave			D		

Conclusion:

Floppy infant/child is a common condition

Detailed history and clinical examination will help in localizing and identifying the probable etiology and will help in reaching to final diagnosis

Work up and investigations should be directed and step-wise approach


Thank You
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