Hypotonia, neuromuscular disorders

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Objectives

- Floppy infant → a common presentation in pediatrics
- SMAs
- Neuropathies
- Muscular dystrophies
- Congenital myopathies
- Myotonic dystrophy
- Myasthenic syndromes
- Malignant hyperthermia

Floppy infant

- A floppy infant is an infant with decreased muscle tone
- Tone is often defined as resistance to passive movement at a joint.
- Muscle tone alterations may also be concluded from a child's posture. ex. frog like position → hypotonia (↳ the lat. aspect of the thigh is on the bed) / scissoring of the legs → spasticity
- Postural tone is the prolonged contraction of antigravity muscles in response to low intensity stretch of gravity
- The maintenance of normal tone requires intact central and peripheral nervous systems So if we have a problem with the CNS or PNS or both → this might lead to abnormal tone

Assessment of the floppy infant

History taking, Look into the following:

- FHx: Three-generation pedigree, consanguinity, recurrent infantile deaths, parental age, Hx of neuromuscular diseases
- Maternal Hx: systemic disease, drug Hx, unrecognized myotonic dystrophy
- Pregnancy: fetal movement, drug exposure, poly-/oligohydramnios, breech presentation → abnormal presentation (It is when a baby is born bottom first instead of head first)
- Delivery: asphyxia, APGAR, resuscitation, cord gases
- Postnatal: feeding, alertness, respiratory effort, spontaneous activity
- Course of floppiness ← بنزل مجروح لما يتنفس
  - ↳ Some disorders start w/ hypotonia and then turns to spasticity (like in CP patients)
  - ↳ Is it proximal or distal hypotonia

* FHx → we take 3 generations because some disorders become more pronounced through generations (such as the case in myotonic dystrophy)

* It's important to take good Hx on pregnancy, as some disorders can start antenataly

* It's very important to ask about Feeding → it has a lot to do with the tone (and it's related to CP)
  ↳ It has to do w/ cordination of feeding (chewing / swallowing) → they'll have misco-ordination
  So we ask if they have problems w/ suckling, is it weak? Can the child swallow well? Is there bulbar involvement? → aspiration بكون جدوتي بيلحج أو بتشرق أو بجيب معه

Clinical signs in a floppy infant

- Frog like posture
- Slipping through the fingers on vertical suspension
- Ragdoll appearance on ventral suspension
- The traction response showing head lag and excessively rounded back
- Associations: Flat occiput, hair loss from occipital region, arthrogryposis, congenital dislocation of the hips and inguinal hernia

↳ describes congenital joint contracture in 2 or more areas of the body

↳ extra : It is usually caused by decreased fetal movements in the womb (so hypotonia in the womb)

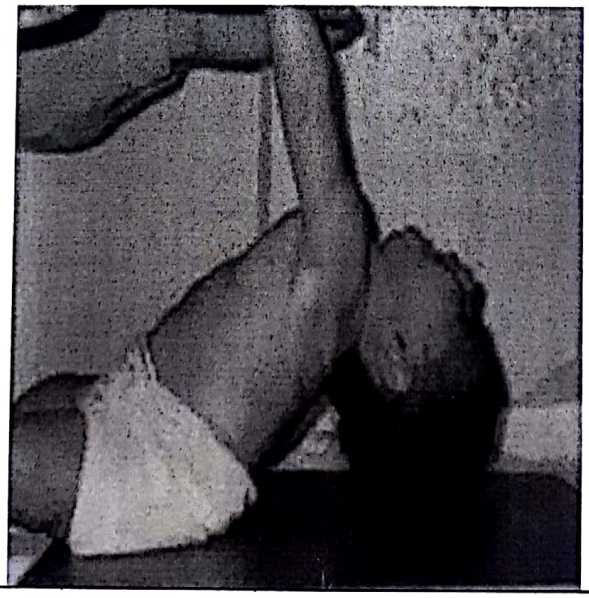
→ Clinical maneuvers to asses tone in an infant :

↳ Vertical suspention
↳ Ventral suspention
↳ The traction response

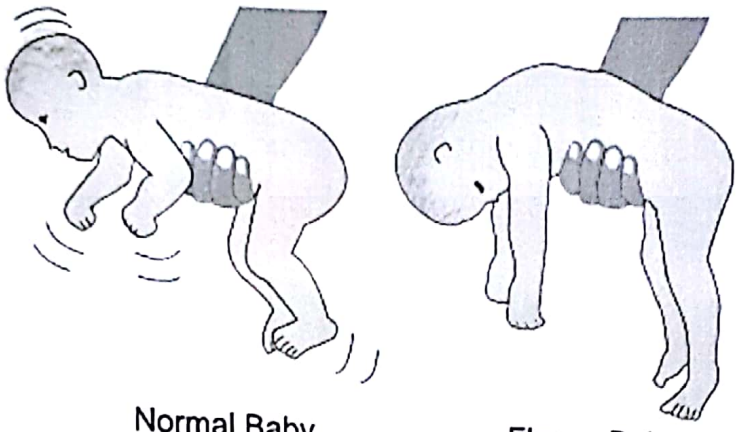
Note : Not every child w/ hip dislocation or hernia has hypotonia

* Note
Good head control is normally seen on 4 months of age

Traction response



Horizontal suspention

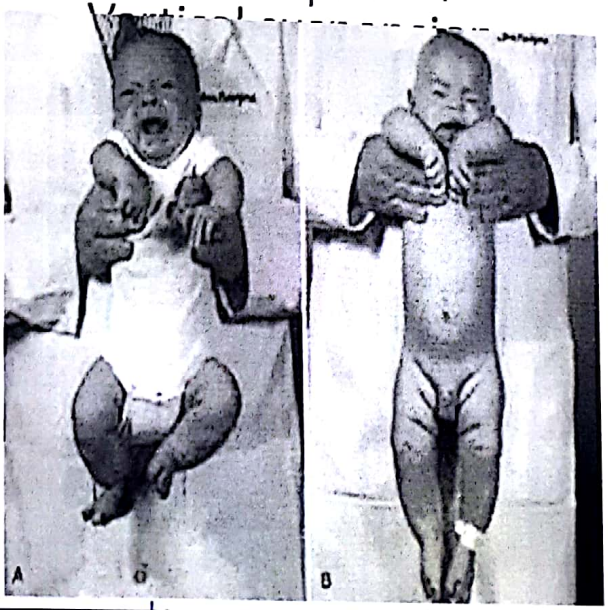


Normal Baby

Floppy Baby

C-shape or U-shape
≡ Ragdoll appearance

Vertical Suspention



*A hypertonic baby the legs often stiffen or cross like scissors

A normal child will have good tone (متوسط حالة) and we will find flexion of the legs

hypotonic baby you feel like he/she is going to slip from your hands

Causes are either due to → UMN / → LMN

- Hypotonia may be due to a disease affecting:

1) the motor unit (→ LMN) (consisting of the anterior horn cell in the spinal cord, its axon in the peripheral nerve, the neuromuscular junction, and the muscle fibers it supplies)

2) the suprasegmental structures or the "upper motor neuron" (the spinal cord, brainstem, cerebellum, and the cerebral hemispheres)

Clues to central nervous system pathology

i.e. to UMN pathology

- Presence of abnormalities of other brain functions(eg. encephalopathy, decrease LOC, seizures)
- Dysmorphic features → they are due to chromosomal abnormalities
- Fisting of the hands
- Scissoring on vertical suspension

(* early signs of spasticity (spasticity indicates UMN pathology))

- Malformations of other organ (ex. hepatosplenomegaly / Cardiomyopathy ... ect) ↳ also think of metabolic disorders related to the UMN
- Normal or brisk deep tendon reflexes (ex. babinski reflex) ↳ like in CP

→ hypotonia means the trunk is hypotonic (regardless of whether the limbs are hypotonic or spastic)

→ When the trunk is hypotonic while the limbs (periphery) are spastic the cause is usually UMN

Central disorders that could result in a floppy infant (Central Hypotonia)

- Hypotonic Cerebral palsy
- Chromosomal disorders including Down's syndrome and Prader Willi
- Genetic disorders like familial dysautonomia and Lowe's syndrome
- Peroxisomal disorders like Zellweger's syndrom
- Metabolic disorders like
- Cerebral malformations
- Inborn errors of metabolism like GM1 gangliosidosis

Clues to motor unit disorders

- Absent or depressed DTR (hyporeflexia or areflexia)
- Fasciculations→only seen in LMN problems, and in some disorders usually in anterior horn cell problems (like in SMA)
- Muscle atrophy
- No abnormalities of other organs

Causes of peripheral weakness

- Neonatal myotonic dystrophy
- Neonatal myasthenia
- Neonatal myopathies eg central core myopathy
- SMAs → affects anterior horn cell
- Hereditary sensorimotor neuropathies
- Infantile botulism
- Congenital myasthenic syndrome
- Muscular dystrophies

Extra Note : TORCH panel test is used to help diagnose infx that could harm the fetus during pregnancy
TORCH is an acrynom for the 5 infx covered by the screening
Toxoplasmosis
Other, including Syphilis
Rubella
Cytomegalovirus (CMV)
Hepes Simplex virus (HSV)

Investigations

- Suspect central cause: our investigations will be according to the presentation

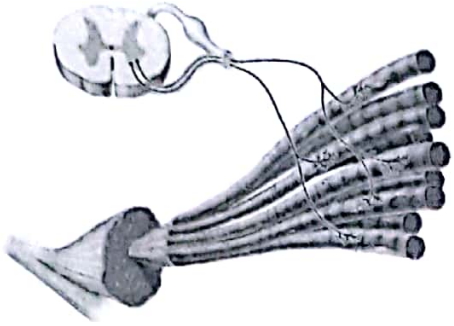
Electrolyte, and glucose, thyroid function, neuroimaging,
EEG, genetic review and karyotype if dysmorphic features,
TORCH, metabolic work up ↪ Chromosomal studies

• If chid has hepalosplenomegaly and jaundice → Liver work up

- Suspect peripheral cause:

CK, neurophysiologic studies, muscle biopsy, molecular genetics as appropriate

Motor unit



Spinal muscular atrophies (SMA's)

- Genetic, AR (Autosomal Ressesive most of the times)

The genetic defects associated with SMA types I-III are localized on chromosome 5q13.

- The incidence of spinal muscular atrophy is about 1 in 10,000 live births with a carrier frequency of approximately 1 in 50
- Progressive degeneration of the anterior horn cells in the spinal cord and motor nuclei in brain stem → Progressive weakness
  → Affects proximal more than distal
- Symmetrical proximal muscle atrophy

* We are going to talk about the common types of SMA which are SMA 1 / SMA 2 / SMA 3

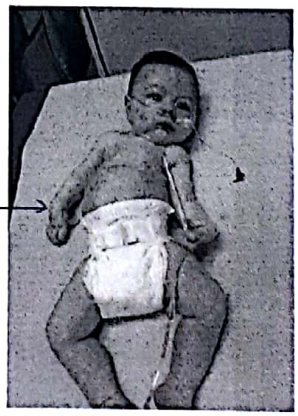
SMA1 (Werding Hoffmann)

- Presentation: 0-6 m (at birth)
- Die<2 y (they usually die before the age of 1 year support ← ممكن يوصلوا سنتين مع الـ)
- Floppy infant
- bell-shaped chest, paradoxical breathing → due to weakness in the chest muscles
- Tongue fasciculation
- Absent reflexes
- Contractures, forearm pronation
- Never sit unsupported

→ ~~The most common of SMAs~~
→ The most severe and the worst type

و عادة مشاكلهم بالتنفس
بتكون أسوأ اشي
Usually the cause of death is due to respiratory causes ... recurrent choking, aspiration, respiratory failure, chest infx ... ect.

SMA1



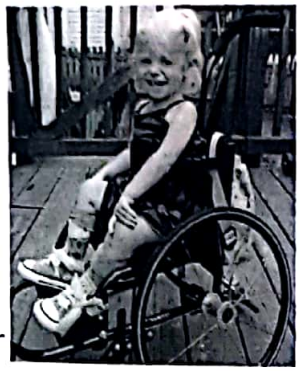
Babies with SMA 1 usually have alert faces.

SMA 1 ← أحسن شوي من

SMA2

- Present: 7-18 m (they present a little bit later than SMA 1)
- Die<20y (live longer than in SMA 1)
- Sit but never walk unsupported
- Deteriorating lung function

They don't have alert faces ←



They sit w/ sth to support their chest to decrease scoliosis ← الطفل hypotonic و حركته قليلة و جسمه ضعيف فبيساعد الطفل عشان اقدر يعيش عنده

Bone deformity

Scoliosis بصير فيها spine و منها ال

pulmonary restriction و إذا زادت كتير ممكن تعمل

↳ including dyspnea and difficulty breathing

* بتزيد مشاكل التنفس لما يناموا فلما يجيك مريض عندو muscular problem

↳ we have to monitor and assess their respiratory system during sleep because during sleep breathing is completely spontaneous

↳ فإذا في مشكلة بتبين أو متح

→ So usually they need support during sleep → we give them CPap or bipap

→ we can also give them a cough assist machine → اللي respiratory problems من الأمراض بتساعد تخفف

ممكن تصير عندهم

SMA3 (Kugelberg-Welander)

- Present >18m
- slowly progressive proximal weakness. Most children with SMA III can stand and walk but have trouble with motor skills, such as going up and down stairs.
- Walks unsupported at some stages
- Bulbar dysfunction occurs late in the disease.

↳ عكس اللي قبل اللي عادة بتكون ال cause of death فبريم

→ SMA 1 → non-sitters
SMA 2 → sitters
SMA 3 → walkers

SMA type IV

- SMA type IV (adult onset): Onset is in adulthood (mean onset, mid 30s).
- In many ways, the disease mimics the symptoms of type III.
- Overall, the course of the disease is benign, and patients have a normal life expectancy.

SMA type zero (Atypical usually)

- Sever ,antenatal onset → Very bad
- Arthrogryposis multiplex congenita
- Ventilator dependent at birth

Investigations

- Genetic testing, Both prenatal and postnatal tests are now commercially available.
- The creatine kinase (CK) level is typically normal in SMA type I and normal or slightly elevated in the other types.
- EMG

Ms. biopsy بتشخصوا عن طريق neuromuscular disorders و ال muscular ← عادة ال
لكن ال SMA صارت من الأشياء اللي بتتشخص genitically
و بطبنا نضط نعمل Ms. biopsy .

Treatment

- Symptomatic therapy: minimizing contractures, preventing scoliosis, good nutritional support, prevent infections
- nusinersen (Spinraza), the first drug approved to treat children (including newborns) and adults with SMA. Nusinersen is an antisense oligonucleotide (ASO) designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency.

The recombinant AAV9-based gene therapy, onasemnogene abeparvovec, was approved in May 2019 for SMA type 1 in children aged 2 years or younger.

→ Ant. horn cells → distal لا proximal بتمشي

proximal ms. weakness فبتعمل

symptoms لا nerves بتيجي بلا المشكلة عنا يكون لما ←
distal to proximal عنا

Neuropathies

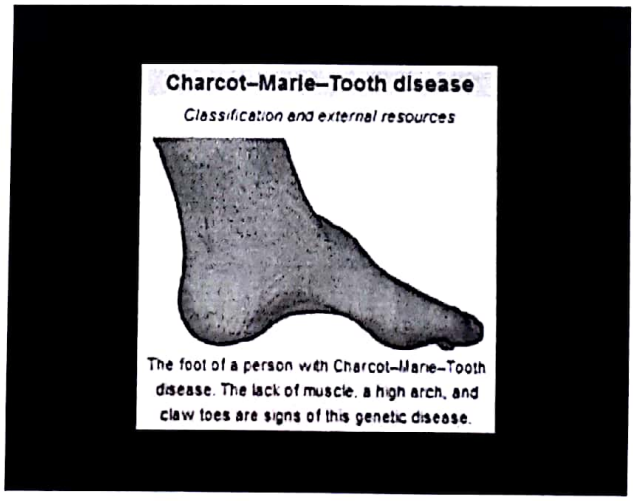
Hereditary and acquired

-Hereditary sensorimotor neuropathies(charcot-marie-tooth disease)

- AD (Autosomal Dominant)
- Onset 2-40 Y, mostly school age
- Slowly progressive, symmetrical, distal muscle weakness and wasting. Affect feet first. Later weakness of intrinsic hand muscles
- Toe walking, falls, later foot drop. Foot deformities: pes cavus, high arch
- Areflexia. Mild distal sensory loss
- Slow nerve conduction velocity, DNA test for duplication in PMP22(70-80%)

↳ +ve in more than 2/3 of the pts

steppage gait ← ممكن يجونا هيول المرضى



Acquired neuropathies
→ Acute
→ Chronic

- Guillian –Barre (acute) (GBS)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)

بجي زي GBS بعدين بتحسن بعدين برجع ← relapse & remission يعني بيجوا هدول ←
العلاج تبعهم عادة بكون موجه لل immunosuppressive therapy
لممكن يوخذوا IVIG أو steroid أو Imuran ... الخ

↳ They may have no disability or they may have some disability

كثير منهم بكونوا misdiagnosed as myopathies ←
وال myopathies ما الهم علاج واضح زي ال CIDP
فكثير مرضى بس يتشخصوا صح و يوخذوا العلاج
يرجعوا يمشوا

⊳ If a child presents w/ acute flaccid paralysis and you suspect poliomyelitis, what do you do?
- We have to inform the ministry of health (this is a public health issue)
- It is diagnosed by taking a stool sample and we look for the polio Ag.

Note: On MRI we might find enhancement of the nerve roots indicating inflammation

Guillian –Barre syndrome
* Important (considered as one of the emergencies)

- Incidence: 1-2/100000 → It is a radiculopathy (in the nerve roots)
- Acute inflammatory demyelinating polyneuropathy
- A prodromal illness within the previous 4 weeks, URTI or GE. Implicated organisms include: mycoplasma, EBV, CMV, influenza A and B, coxsacki virus. Combylobacter jejuni
- Progressive motor weakness, ascending (distal to proximal), involving more than one limb, relative symmetry, mild sensory involvement. Progression of the weakness max after 2 wk in 50% of the patient, 3 wk in 80% and 4 wk in the rest
- Areflexia, autonomic dysfunction
- CSF: elevated protein ,WBC less than 10
- Nerve conduction abnormality

⊳ Albuminocytogenic dissociation

↳ Rate of progression may be related to the prognosis
→ In all pts w/ AFP, we have to recognise respiratory and bulbar weakness ASAP.

حفظ غير المكتوب أمثلة عالنت إذا بتحبوا تشوفوهم

* Presents as Acute Flaccid Paralysis (AFP)
- started in a period of < 4 weeks (i.e started within hours to a max of 4 wks)
- Hypotonia
- Weakness

⊳ Causes of Acute Flaccid Paralysis:
- spine – transverse myelitis
- Ant. horn – Acute Ant. poliomyelitis
- nerves – GBS
- ms. – Myositis
- NMJ – Myasthenia gravis

GBS, cont..

→ like GBS but w/ Cranial nerve involvement most commonly opthalmoplegia

- Miller-fisher syndrome

-Probably a variant of GBS

-Triad of ataxia, ophthalmoplegia and areflexia

-Brain stem encephalitis

- Management: → Monitor and support

-Careful monitoring of the respiratory function and bulbar Fx

-Intravenous immunoglobulin

-Plasmaphoresis

Muscular dystrophies- Dystrophinopathies

- A number of clinical phenotypes result from mutations in the dystrophin gene at Xp21: Duchenne/Becker muscular dystrophy, X-linked cardiomyopathy and myalgia and cramps
- This leads in Duchenne/Becker to decreased muscle content of the structural protein dystrophin: in DMD the dystrophin content is 0-5% of normal, and in BMD the dystrophin content is 5-20% of normal

So in DMD the dystrophin protein is lower than in BMD

Clinical presentation

- The initial feature in most boys with DMD is a gait disturbance → Waddling gait
- Onset always before 5y, often before 3y
- Toe walking and frequent falling
- Often , Hx of delayed achieving of motor milestones, global developmental delay is not uncommon
- Intellectual impairment
- Symmetric proximal weakness. Waddling gait, Gower sign is present, increased lordiosis
- Calf muscle hypertrophy (Pseudohypertrophy)

بتغلبو ا بالطلعة و النزلة عل الدرج

Pattern of weakness →

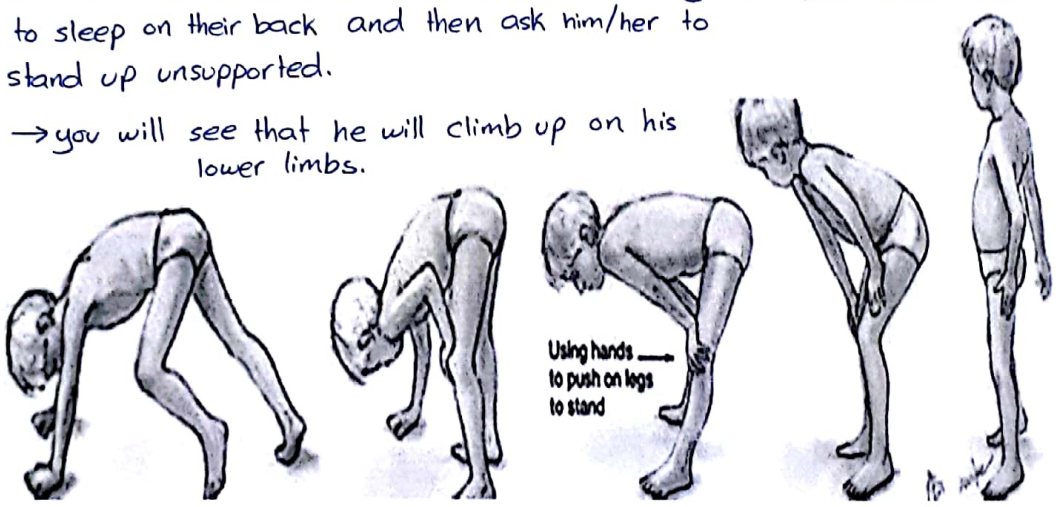
Note: The lower limbs are affected more than the upper limbs

Gower sign

→ Indicates proximal ms. weakness

*Ask the child to sit down and extend their legs (يقعد و يمد رجليه) or to sleep on their back and then ask him/her to stand up unsupported.

→ you will see that he will climb up on his lower limbs.



DMD..

وهو ممكن أبكر شوي

- Loss of independent ambulation by 13y (in BMD by 16y), wheelchair 8-12 y old *It is a progressive disorder
- Cardiomyopathy, annual screening *Usually we do echo and screening once every 2 yrs before the age of 10 and after 10 yrs of age once yearly.
  heart ms. الـ على خشيك ضروري
- Scoliosis
- Respiratory: deterioration of vital capacity to less than 20% of normal to nocturnal hypoventilation → so they might need support during sleep.
- Leading cause of death is cardio/respiratory complications.

Diagnosis

- CK is 10 times the upper limit of normal then declines about 20% per year
  why? because we're running out of muscles
- Gene mutation → so we can diagnose genetically
- Muscle biopsy: little or no dystrophin staining

Management:

-Prednisone → Once Ck is high we can use it, it may slow down the progression, but it doesn't stop it.

-Aim is to maintain function and prevent contraction; orthoses, scoliosis surgery

-Psychological support /Social and financial support as well for the child and the parents

BMD

أخف شوي من DMD

- Presentation similar to DMD but variable severity/onset
- slow progression
- Life expectancy is longer
- Biopsy: patchy dystrophin staining

Other muscular dystrophies:
-Limb girdle muscular dystrophy
-Facioscapulohumeral dystrophy

Congenital muscular dystrophies

- A group of conditions presenting at birth or early childhood with hypotonia, weakness and contractions
- static or only slight progression
- CK normal or slightly elevated
- Some are associated with disorders of myelin or neuronal migration or congenital eye abnormalities (eye, muscle, brain disease)

Congenital myopathies

- Hypotonia and motor delay
- Static or slowly progressive
- CK normal
- Muscle biopsy: myopathic without dystrophic changes

-Central core disease

-Minicore disease

-Nemalin rod myopathy

-Centronuclear myopathy

Myotonic dystrophy

- Multisystem disorder transmitted by autosomal dominant inheritance with variable penetrance why ?

1-Amplification or "trinucleotide-repeat"

-severity depends on length of expansion → the longer the more severe

2-Anticipation: repeat length expand in next generation, so more sever disease with earlier onset in the newer generation

Myotonic dystrophy..

- Cataract, ptosis
- Frontal baldness
- Myopathic face
- Polyhydramnios, reduced fetal movement
- Hypotonia, nn. respiratory distress
- Arthrogryposis
- Myotonia (not at birth):delayed relaxation (prolonged contraction) voluntary contraction[1] → فمثلاً بس تجرب تسلم على مريض بسكو على ايدك و بتعوفش تسحبها ... بدو وقت ليرجع يفك ايدو
- Learning difficulties
- Endocrinopathies: insulin resistance, gonadal failure (sterility)

Myotonic dystrophy

Anticipation of the CTG-repeat expanion

	Repeats (N<30)	Course	Symptoms
grandmother	150	mild	cataract
mother	450	moder ate	Myopathic face, dysarthria
child	3000	sever	nn. Resp.distress, mental retardation

Diagnosis

- Clinical features
- Family history
- Molecular genetic study

Supported by clinical presentation

Myasthenic syndromes

→ Autoimmune
→ Genetic

- Disorders in neuromuscular transmission due to autoantibodies or gen defect
- Weakness and fatigability on exercise

Related to exercise and diurnal variation

Myasthenia gravis (MG)

- Onset 1-17 y
- Insidious or sudden onset(with febrile illness)
- M:f (1:4)
- weakness (proximal)and fatigability, with diurnal variation
- Ptosis, ophthalmoplegia → when you have this think about myasthenia
- Dysphagia, dysphonia, dyspnea (Respiratory and bulbar ms. weakness)
- Antibodies:80% acetylcholine receptor (AChR) antibodies positive
  14% muscle specific kinase (MuSK) antibodies positive
- Thymoma 10%
- Dx: AB, neurophysiology, Tensilon test or trial of pyridostegmine
- Rx: anticholinesterase, immunotherapy in sever cases(prednisolone, azathioprine, IVIG, plasma exchange ↳ during the acute episode

Transient neonatal myasthenia

↳ Seen in the babies of mothers w/ MG

- Transplacental transfer of AChR antibodies
- 10-15% of myasthenic mothers
- Hypotonia, weakness, bulber and resp. insufficiency within 4 days of birth ↳ dysphagia / poor feeding / respiratory distress
- Dx: AB, response to cholinesterase inhibitors

Congenital myasthenic syndrom

- Genetic disorder, AR (Autosomal Recessive)
- Onset 0-24m (before 2 yrs of age usually) → related to bulbar ms. weakness
- Hypotonia, weakness, bulber, resp. weakness, weak cry, feeding difficulties, recurrent chest infections, episodic apnea
- Dx: family Hx, negative AB, response to anticholinesterases, electrophysiology, molecular studies

Drugs that impair neuromuscular junction transmission and may increase weakness

- Aminoglycosides. Tobramycin. Gentamycin. ...
- Fluoroquinolones. Ciprofloxacin. Norfloxacin. ...
- Tetracyclines. Clindamycin. ...
- Penicillins - considered safe, though anecdotes of ampicillin causing resp depression.
- Macrolides. Azithromycin. ...
- Quinolones.
- Ritonavir.

Malignant hyperthermia

هاي التغيرات عادةتغلب تبصير قبل الـ Hyperthermia

- Presents as generalized muscle rigidity, tachycardia, tachypnea, rhabdomyolysis, acidosis, hyperkalemia, myoglobinuria, raised CK and hyperthermia(occurs late)
- Triggers: inhalational anesthetics(isoflurane, desflurane..) , depolarizing muscle relaxant(succinylcholine)
- Associated with: dystrophin deficient muscular dystrophies, myotonic dystrophy
- Rx: ICU management of fluid balance and rhabdomyolysis and possible renal involvement, Dantrolene → The antidote
- **Very important** to warn patients with neuromuscular disorders of the increased risk of anesthetic reactions, so to inform anesthetists before GA and appropriate anesthetic agents can be used

General Anesthesia

Thank you