Hypotonia, neuromuscular disorders

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Objectives

- Floppy infant
- 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.
- 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

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
- Delivery: asphyxia, APGAR, resuscitation, cord gases
- Postnatal: feeding, alertness, respiratory effort, spontaneous activity
- Course of floppiness

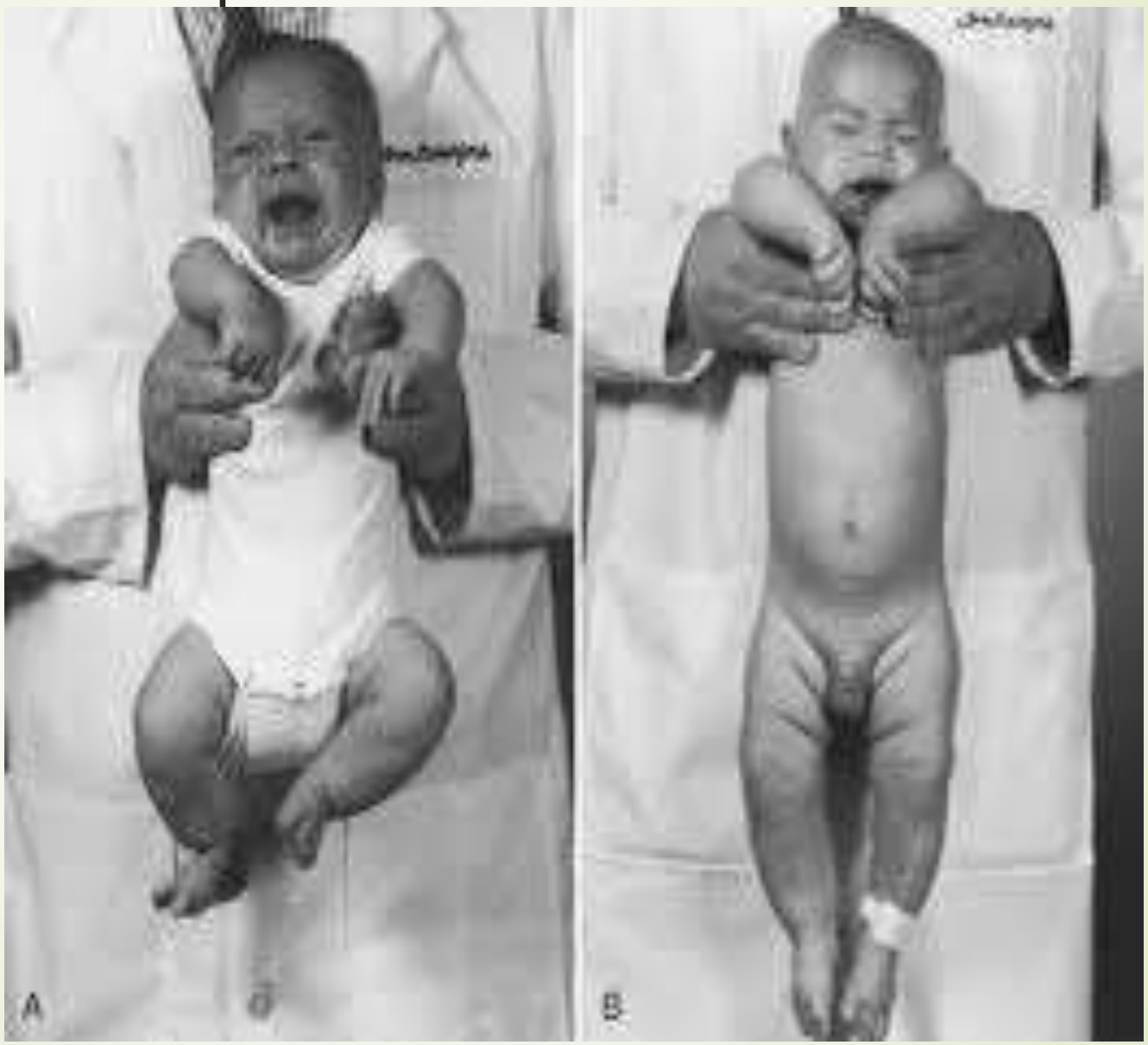
Clinical signs in a floppy infant

- 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

Traction response

Horizontal suspention

Vertical suspension



Causes

- Hypotonia may be due to a disease affecting:

1) the motor unit (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

- Presence of abnormalities of other brain functions(eg. decrease LOC, seizures)
- Dysmorphic features
- Fisting of the hands
- Scissoring on vertical suspension
- Malformations of other organ
- Normal or brisk deep tendon reflexes

Central disorders that could result in a floppy infant

- 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
- Fasciculations
- Muscle atrophy
- No abnormalities of other organs

Causes of peripheral weakness

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

Investigations

- Suspect central cause:

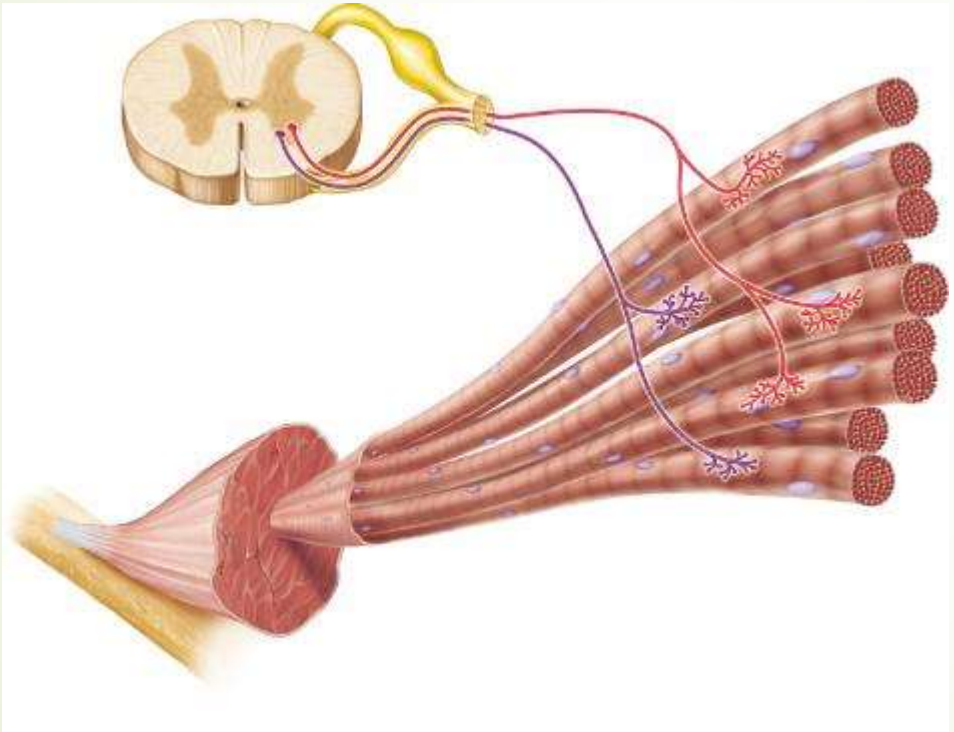
Electrolyte, and glucose, thyroid function, neuroimaging,

EEG, genetic review and karyotype if dysmorphic features, TORCH, metabolic work up

- Suspect peripheral cause:

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

Motor unit



Spinal muscular atrophies

- Genetic, AR

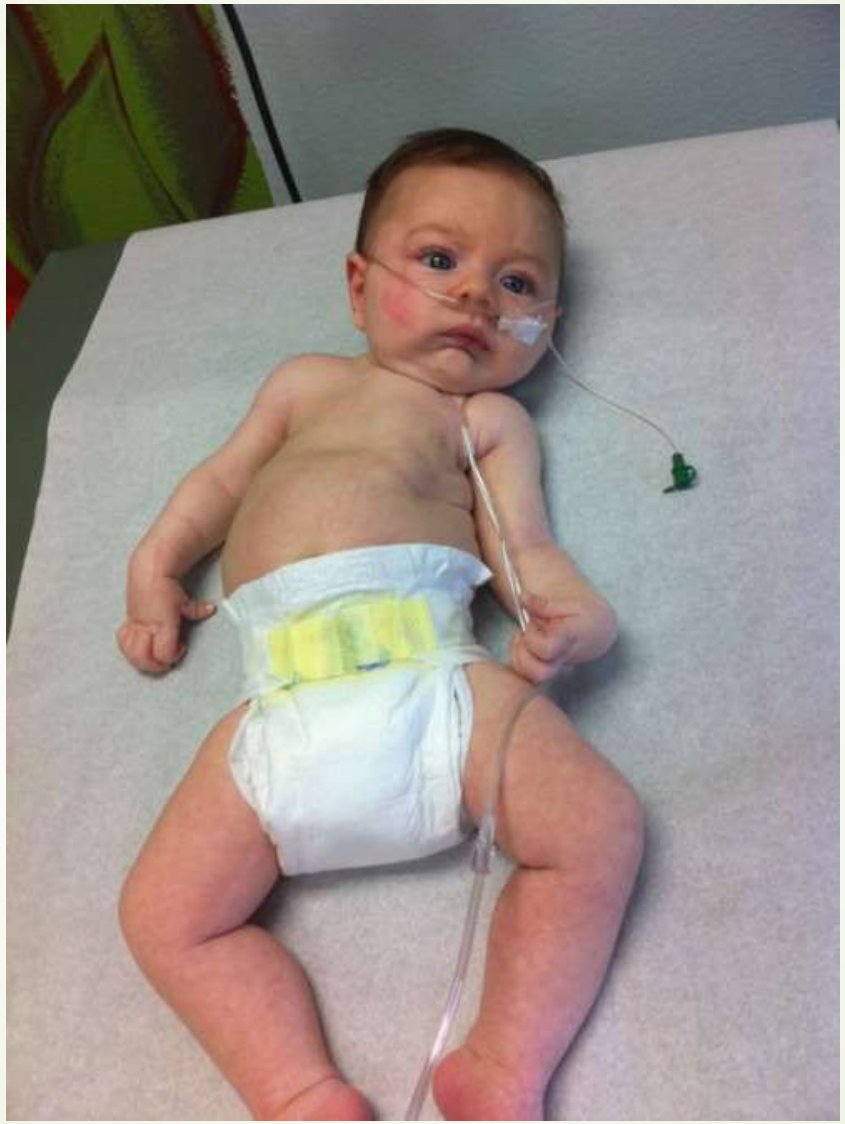
The genetic defects associated with SMA types I-III are localized on chromosome 5q13.

- 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
- Symmetrical proximal muscle atrophy

SMA1 (Werding Hoffmann)

- Presentation: 0-6 m
- Die<2 y
- Floppy infant
- bell-shaped chest, paradoxical breathing
- Tongue fasciculation
- Absent reflexes
- Contractures, forearm pronation
- Never sit unsupported

SMA1



SMA2

- Present: 7-18 m
- Die<20y
- Sit but never walk unsupporte
- Deteriorating lung function

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.

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

- Sever ,antenatal onset
- 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

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.

Neuropathies

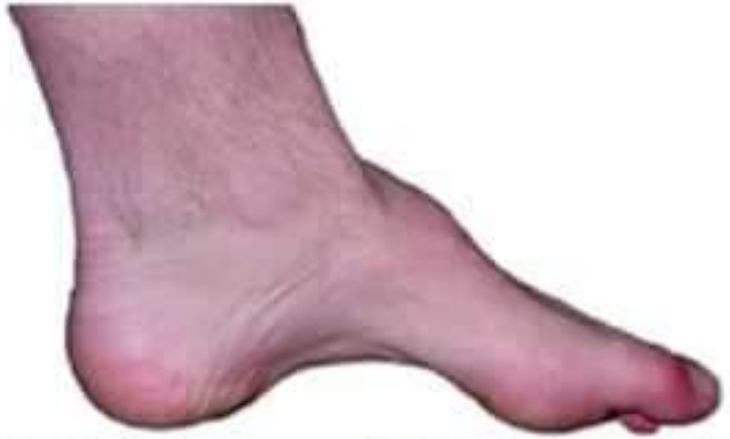
Hereditary and acquired

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

- AD
- 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%)

Charcot–Marie–Tooth disease

Classification and external resources



The foot of a person with Charcot–Marie–Tooth disease. The lack of muscle, a high arch, and claw toes are signs of this genetic disease.

Acquired neuropathies

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

Guillian –Barre syndrome

- Incidence: 1-2/100000
- 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, 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

GBS, cont..

- Miller-fisher syndrome

-Probably a variant of GBS

-Triad of ataxia, ophthalmoplegia and areflexia

-Brain stem encephalitis

- Management:

-Careful monitoring of the respiratory function

-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

Clinical presentation

- The initial feature in most boys with DMD is a gait disturbance
- 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

Gower sign

DMD..

- Loss of independent ambulation by 13y (in BMD by 16y), wheelchair 8-12 y old
- Cardiomyopathy, annual screening
- Scoliosis
- Respiratory: deterioration of vital capacity to less than 20% of normal to nocturnal hypoventilation
- Leading cause of death is cardio/respiratory complications.

Diagnosis

- CK is 10 times the upper limit of normal then declines about 20% per year
- Gene mutation
- Muscle biopsy: little or no dystrophin staining

Management:

-Prednisone

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

-Psychological support

BMD

- 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

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

-Amplification or “trinucleotide-repeat”

-severity depends on length of expansion

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

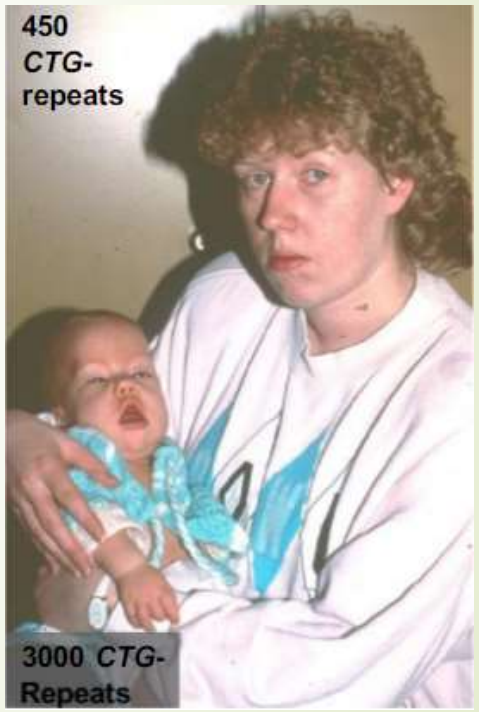
Myotonic dystrophy..

- 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
- Learning difficulties
- Endocrinopathies: insulin resistance, gonadal failure

Myotonic dystrophy

Anticipation of the CTG-repeat expanion

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



Diagnosis

- Clinical features
- Family history
- Molecular genetic study

Myasthenic syndromes

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

Myasthenia gravis

- Onset 1-17 y
- Insidious or sudden onset(with febrile illness)
- M:f (1:4)
- weakness (proximal)and fatigability, with diurnal variation
- Ptosis, ophthalmoplegia
- Dysphagia, dysphonia, dyspnea
- 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

Transient neonatal myasthenia

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

Congenital myasthenic syndrome

- Genetic disorder, AR
- Onset 0-24m
- 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

- 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
- **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

Thank you