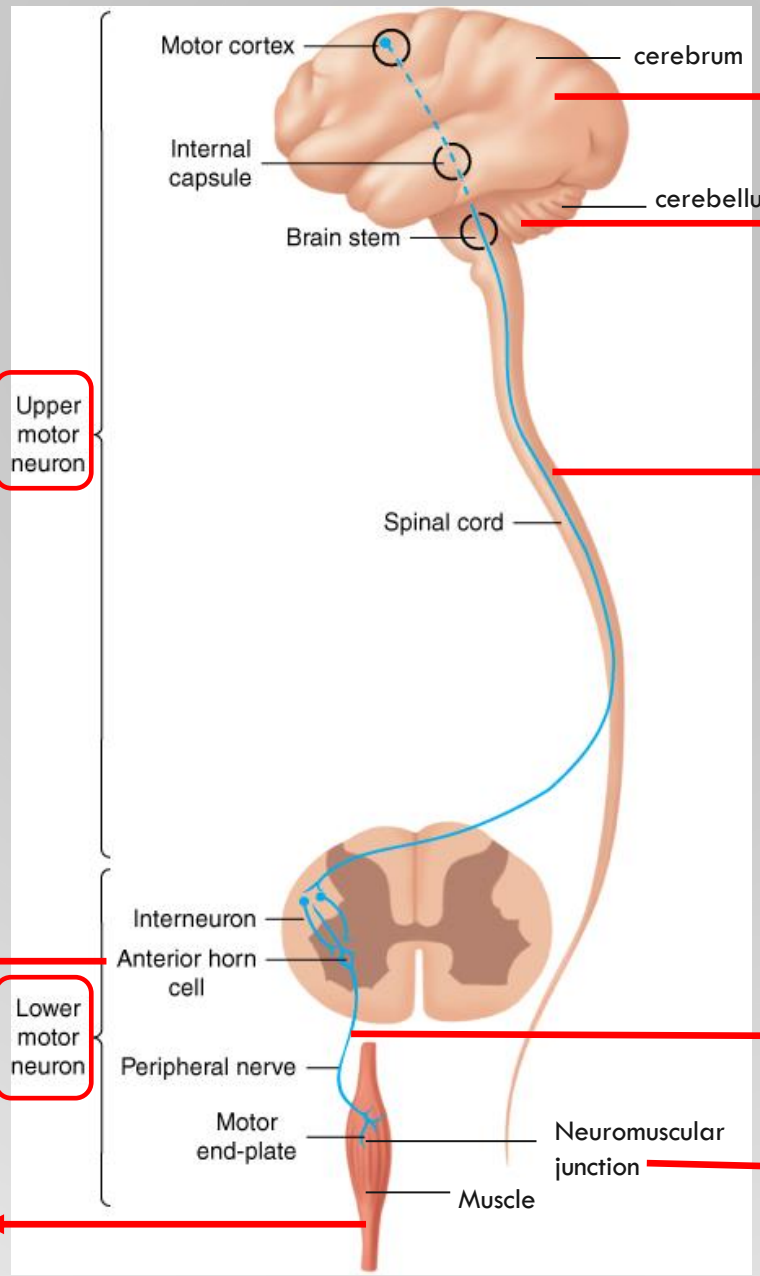
LOCALIZATION – BASED

NEUROLOGICAL DISEASES IN CHILDREN

AMAL ABU LIBDEH, MD

PEDIATRIC NEUROLOGY



-Autoimmune encephalitis

-ADEM

-Opsoclonus Myoclonus Ataxia Syndrome

-Transverse Myelitis

-Acute Flaccid Myelitis

-Poliomyelitis

-Spinal Muscular Atrophy

-Gullain Barre syndrome

-Charcot Marrie Tooth

-Duchenne Muscular Dystrophy

-Dermatomyositis

-Myotonic dystrophy

-Myasthenia Gravis

-Botulism

UMN vs LMN

Features	Upper motor neuron lesion	Lower motor neuron lesion
Site of the lesion	Cerebrum hemispheres, cerebellum, brain stem, or spinal cord	Anterior horn cell, roots, nerves, neuromuscular junction, or muscles
Muscle weakness	Quadriplegia, hemiplegia, diplegia, triplegia	Proximal (myopathy) Distal (neuropathy)
Muscle tone	Spasticity/rigidity	Hypotonia
Fasiculations	Absent	Present (tongue)
Tendon reflexes	Hyperreflexia	Hyporeflexia/areflexia
Abdominal reflexes	Absent (depending on the involved spinal level)	Present
Sensory loss	Cortical sensations	Peripheral sensations
Electromyography	Normal nerve conduction Decreased interference pattern and firing rate	Slow nerve conduction Large motor units Fasciculations and fibrillations

INTRODUCTION

- Autoimmune neurological disorders are a heterogeneous group of rare disorders that can affect the central or peripheral nervous system at any level.
- These can affect the brain, spinal cord, nerve roots, peripheral nerves, neuromuscular junction, and muscle.
- Presentation is typically acute or subacute in onset, usually with a history of preceding infection.
- Early recognition may lead to early initiation of immunotherapy and an improvement in long-term neurologic outcomes.

OUTLINE

- Autoimmune encephalitis
- Acute Disseminated Encephalo Myelitis (ADEM)
- Opsoclonus myoclonus Ataxia Syndrome (OMAS)
- Transverse Myelitis (TM)
- Acute Flaccid Myelitis (AFM)
- Guillain Barre Syndrome (GBS)

OUTLINE

- **Autoimmune encephalitis**
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AUTOIMMUNE ENCEPHALITIS

- An immune-mediated inflammatory disorder of the brain.
- Subacute presentation.
- Symptoms: encephalopathy, psychosis, movement disorders, seizures, focal neurologic deficits, and autonomic nervous system dysfunction.
- Symptoms in children may be subtle, such as behavioral changes or sleep disturbances.

AUTOIMMUNE ENCEPHALITIS

Table 2 Criteria for "possible autoimmune encephalitis" (simplified according to Panel 1 in [25])

All three must be fulfilled:

1 Subacute onset (< 3 months) of working memory deficits (short-term memory loss), altered mental status (decreased or altered level of consciousness, lethargy or personality change) or psychiatric symptoms

2 ≥1 of the following:
- New focal CNS findings
- Seizures not explained by a previously known seizure disorder
- CSF pleocytosis (white blood cell count > 5/μl)
- MRI features suggestive of encephalitis

3 Reasonable exclusion of alternative causes[a]

[a]CNS infections, septic encephalopathy, metabolic encephalopathy, drug toxicity (Including use of illicit drugs, direct neurotoxic effect of prescribed drugs or through induction of seizures, posterior reversible encephalopathy, idiosyncratic reaction [e.g. neuroleptic malignant syndrome], drug interaction [e.g. serotoninergic syndrome] or drug withdrawal), cerebrovascular disease, neoplastic disorders, Creutzfeldt-Jakob disease, epileptic disorders, rheumatologic disorders (e.g., lupus, sarcoidosis, other), Kleine-Levin syndrome, Reye syndrome (children), mitochondrial diseases, inborn errors of metabolism (children)

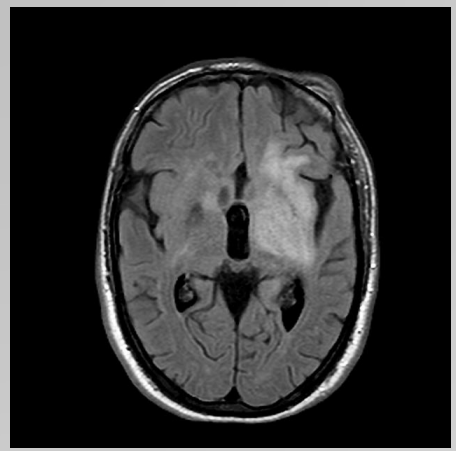
AUTOIMMUNE ENCEPHALITIS

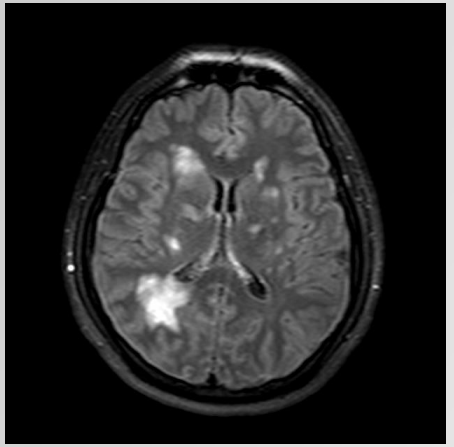
- **Investigations:**
- CSF: inflammatory changes (elevated protein, lymphocytic pleocytosis, elevated immunoglobulin G (IgG) index, unique oligoclonal bands)
- Labs: antibodies (anti NMDA, Anti GAD 65, etc)
- EEG: abnormal in 90 % of patients, generalized slowing or focal abnormalities.
- MRI: changes suggestive of inflammatory disease.

AUTOIMMUNE ENCEPHALITIS

- Example: Anti- NMDA encephalitis.
- Elevated serum titers of anti-NMDA antibodies

Examples of MRIs of patients with NMDA encephalitis





AUTOIMMUNE ENCEPHALITIS

- **Treatment:**
- First-line treatment: IV steroids, IV immunoglobulin (IVIG), and/or plasmapheresis.
- Other treatment options: Rituximab, and cyclophosphamide.
- **Outcome:**
- Patients may have residual symptoms.
- They are at risk of relapse.

OUTLINE

- Autoimmune encephalitis
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- Opsoclonus myoclonus Ataxia Syndrome (OMAS)
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ADEM (ACUTE DISSEMINATED ENCEPHALOMYELITIS)

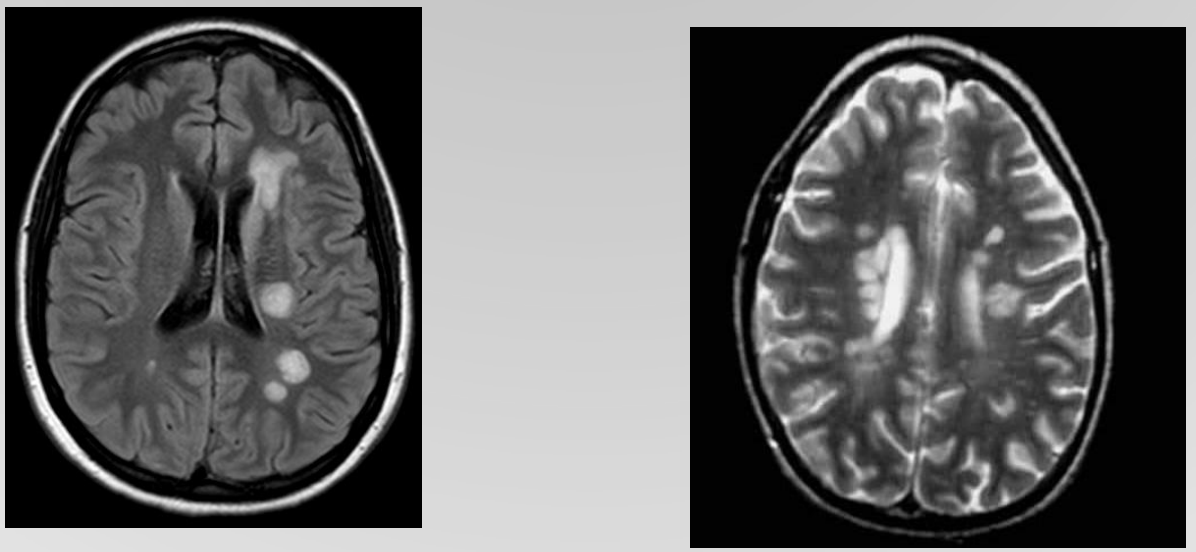
- It is an immune-mediated inflammatory demyelinating condition that predominately affects the white matter of the brain and spinal cord.
- Typically preceded by a febrile infection or an immunization. More common in winter months October to March.
- Typically in pre-pubertal children (more than 80 % are in children less than age 10 years).

ADEM (ACUTE DISSEMINATED ENCEPHALOMYELITIS)

- It presents with fever, an acute-onset encephalopathy, associated with polyfocal neurologic deficits.
- Symptoms reported in children are variable. Encephalopathy ranges from mild sleepiness and behavioral change to lethargy and coma.
- Neurologic symptoms include ophthalmoplegia, vision loss, ataxia, weakness, movement disorders, and autonomic dysfunction.
- Physical exam could show a wide variety of cranial nerve abnormalities. Hyperreflexia, clonus, and upgoing toes are present in 85% of cases. Also limb weakness and ataxia.

ADEM (ACUTE DISSEMINATED ENCEPHALOMYELITIS)

- **Investigations:**
- CSF: inflammatory changes (elevated protein, lymphocytic pleocytosis)
- MRI: diffuse, poorly demarcated large lesions predominantly involving white matter. Gray matter may also be involved.



Examples of MRIs of patients with ADEM

ADEM (ACUTE DISSEMINATED ENCEPHALOMYELITIS)

- **Treatment:**
- IV steroids, IV immunoglobulin (IVIG).
- **Outcome:**
- Typically self-limiting, carries an excellent prognosis. with most patients making full recovery. Recovery is poorest in children younger than 2 years, patients with myelitis, and those who have significant edema of the brain or spinal cord.
- Typically monophasic, but a subset of patients may have anti-myelin oligodendrocyte glycoprotein (MOG) antibodies and are more likely to have additional attacks.

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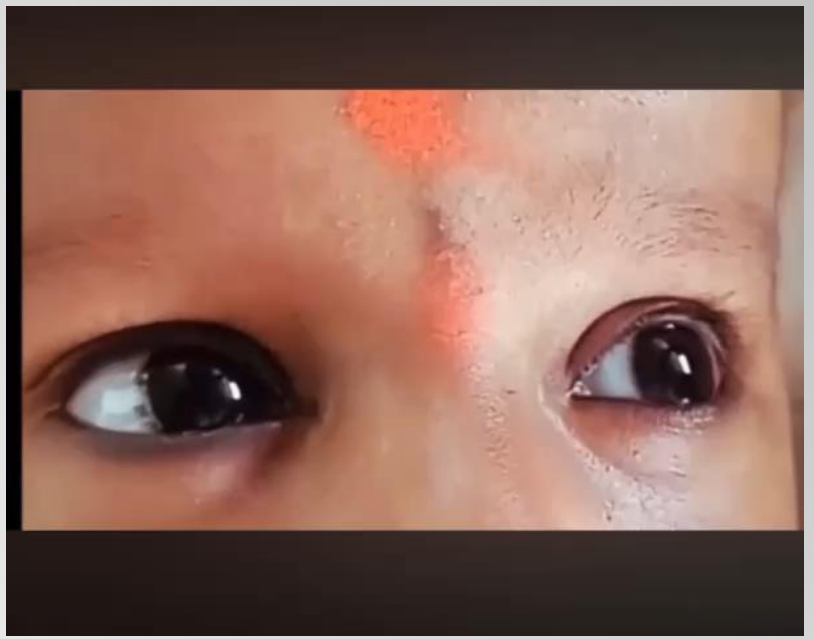
OPSOCLONUS MYOCLONUS ATAXIA SYNDROME

- Rare immune mediated disease.
- **Etiology:**
- 50 % of children have neuroblastoma. The rest thought to be post-infectious or autoimmune.

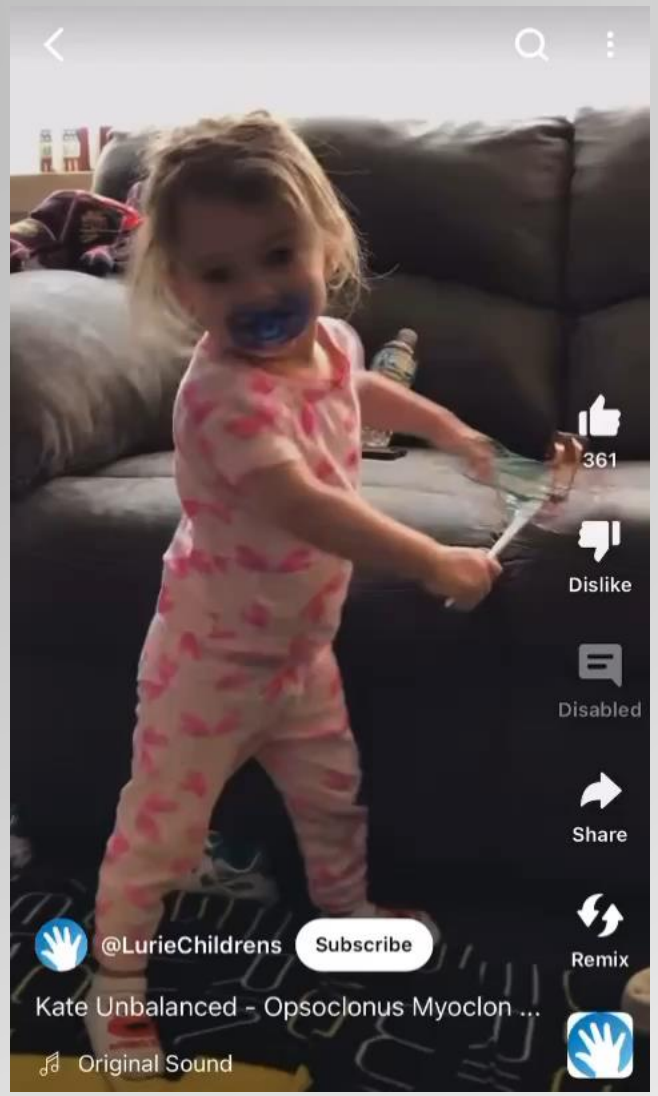
OPSOCLONUS MYOCLONUS ATAXIA SYNDROME

- **Presentation:**
- Opsoclonus
- Myoclonus
- Ataxia (cerebellar) :The gait is typically wide based, unsteady. Speech abnormalities such as fluctuations in clarity. Posture while sitting unsupported may be difficult to maintain (titubation). Coordination of voluntary movements may be impaired, as seen on finger-nose testing (dysmetria) and during rapid alternating movements (dysdiadochokinesia). Hypotonia, action tremor, and end-gaze nystagmus may also occur.
- Behavioral issues : mood issues, sleep disturbances, irritability, etc.

Opsoclonus

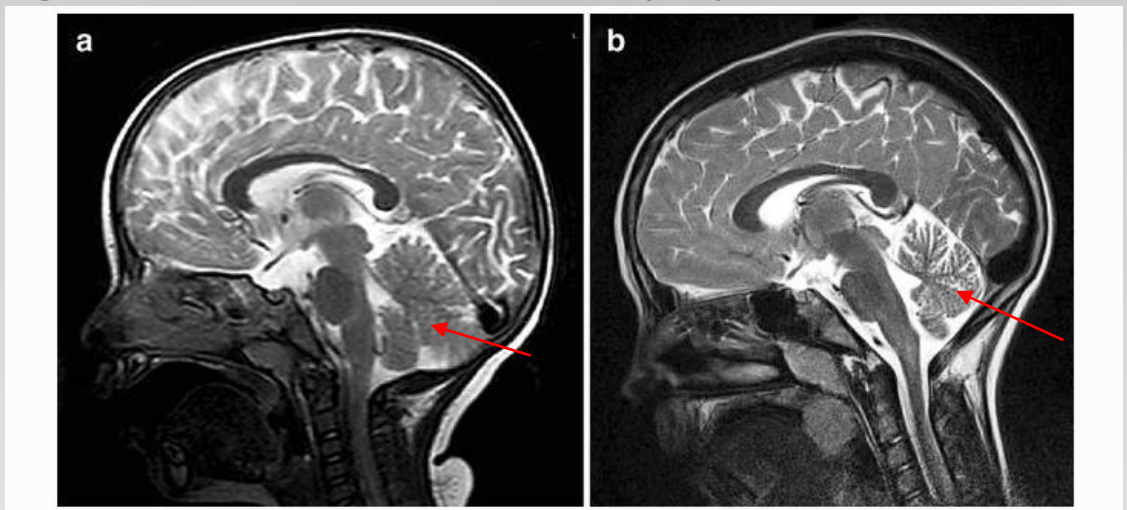


Myoclonus and Ataxia



OPSOCLONUS MYOCLONUS ATAXIA SYNDROME

- **Investigations:**
- Serum and CSF antibodies
- Body imaging, US, CT, MRI (best)
- Brain MRI: Progressive Cerebellar atrophy



Sagittal T2-weighted cranial magnetic resonance images at onset of opsoclonus-myoclonus syndrome (**a**) and 5 years later (**b**), showing mild cerebellar atrophy with widened sulci and extracerebellar spaces

OPSOCLONUS MYOCLONUS ATAXIA SYNDROME

- **Treatment:**
- IV steroids, IV immunoglobulin (IVIG), treatment of underlying etiology
- **Outcome:**
- Depends on etiology, and time to diagnosis.

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TRANSVERSE MYELITIS

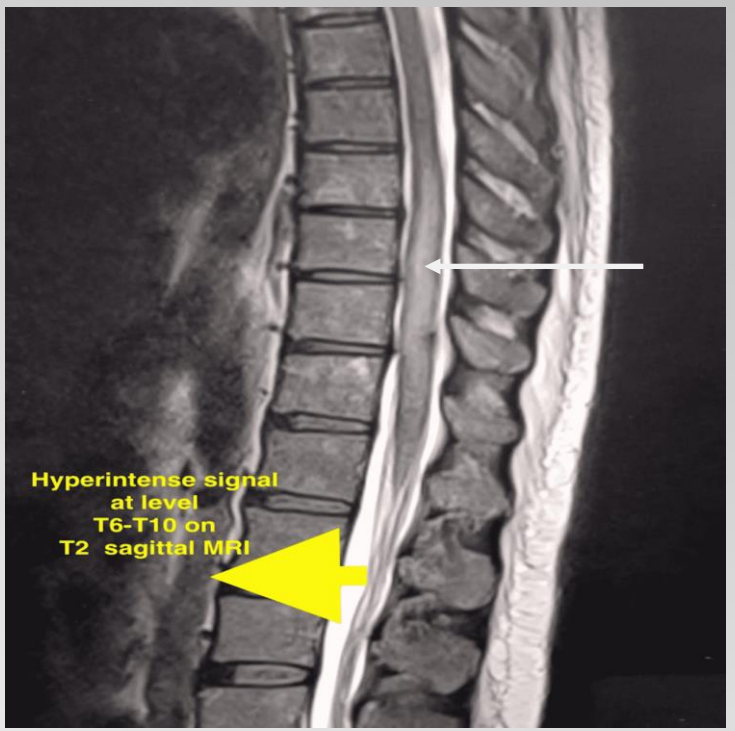
- A rare immune-mediated inflammatory demyelinating disorder involving the spinal cord.
- Age distribution is bimodal, primarily affecting children under 5 and older than 10 yr of age
- A preceding infection or vaccination is reported in up to 66% and 28% of children respectively, during 30 days before the onset of the disease.

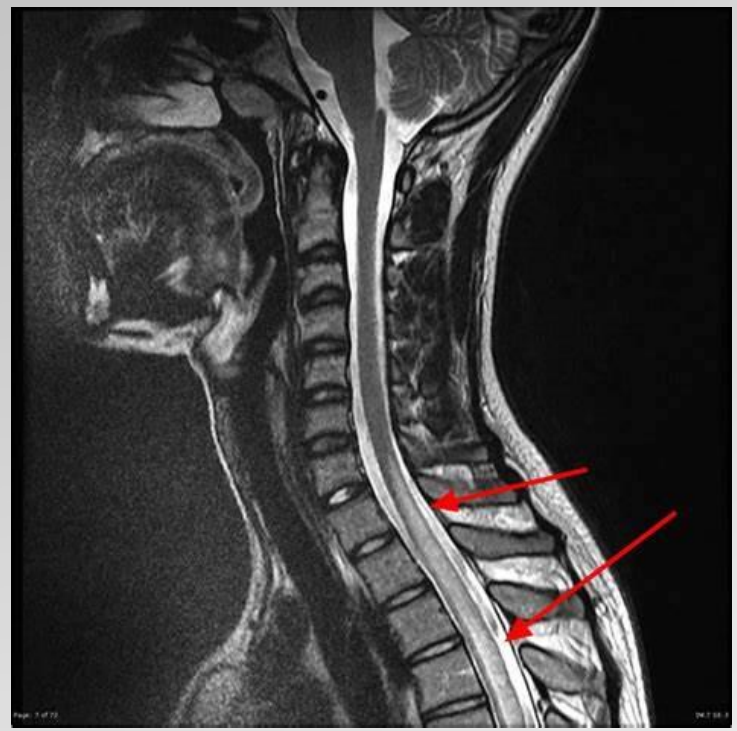
TRANSVERSE MYELITIS

- It is characterized by a relatively acute onset of motor, sensory, and autonomic dysfunction.
- The first presentation in children is usually back pain.
- Rapidly progressive motor deficits develop in the lower extremities. Initially, flaccid paresis and decreased deep tendon reflexes are often detected, but subsequently, it evolves to a state of increased tone and increased DTRs below the level of lesion. Upper extremities also may be involved in the spinal cord lesion is in the thoracic region. Sensory deficits such as pain, burning paresthesia, hyperesthesia, and numbness also occur. Variation in body temperature, with instability of respiratory rate and heart rate. Sphincter dysfunction, constipation, and urinary symptoms such as retention, urgency, and incontinence can happen.
- **Sensory level** is detectable in the majority of patients, mostly in the thoracic region. The border of sensory level establishes the level of spinal cord involvement. Acute complete transverse myelitis (ACTM) includes symmetric motor, sensory, and autonomic dysfunction on both sides below the level of the lesion.

TRANSVERSE MYELITIS

- **Investigations:**
- CSF: inflammatory changes (elevated protein, lymphocytic pleocytosis)
- MRI: enhancing lesions in the spinal cord in one or two vertebral segments.





TRANSVERSE MYELITIS

- **Treatment:**
- Mainly IV steroids, also IV immunoglobulin (IVIG) and plasmapheresis.
- **Outcome:**
- It is potentially a devastating disorder with variable outcomes. Outcome in children is better than adults, as almost 50% of children obtain recovery after 2 yr .
- Worse outcome is associated with: younger age at the onset of the disease (worst in infants), rapid onset of symptoms, shorter time (less than 24 h) to maximal deficit, complete paraplegia, need for assisted ventilation, longer time to treatment, absence of CSF pleocytosis, higher border of sensory level.
- Factors that predict recurrence: longitudinally extensive lesions in spinal cord, brain lesions on MRI, the presence of 1 or more autoantibodies (ANA, ds DNA, phospholipid antibody, C-ANCA), Oligoclonal bands in CSF, presence of NMO-IgG (anti-Aquaporin-4)antibody, and female sex.

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ACUTE FLACCID MYELITIS

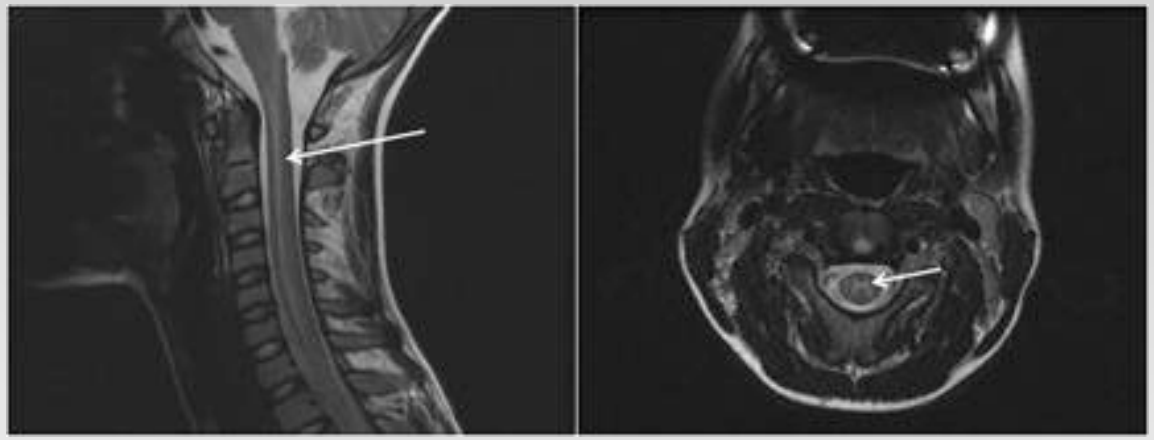
- It is an acquired spinal cord disorder affecting anterior horn cells.
- It presents with the rapid onset of weakness in one or more limbs.
- It resembles polio and mainly affects children. First described in 2014.
- The median age is 6 years.
- Enterovirus EV-D68 is thought to be the main virus associated with this condition. Other viruses include EV- D71, and coxsackievirus.

ACUTE FLACCID MYELITIS

- Most children experience a prodrome of fever and respiratory symptoms, such as cough, rhinorrhea, or pharyngitis. Neurologic symptoms generally begin 1 to 10 days after the onset of the prodrome. These consist of acute onset of flaccid limb weakness accompanied by hyporeflexia or areflexia.
- Onset typically is asymmetric and favors the upper limbs and proximal muscles. Patients also may have weakness of the neck, trunk, diaphragm, or other respiratory muscles.
- Some have cranial nerve dysfunction, bowel or bladder dysfunction, and/or sensory alterations
- Most patients require hospitalization, and some need intubation.

ACUTE FLACCID MYELITIS

- **Investigations:**
- CSF: pleocytosis. (typically the virus cannot be detected in CSF)
- Respiratory samples may detect Enterovirus D68, and stool samples may indicate enterovirus A71. (should also check for polio in stool)
- Electromyography (EMG) and nerve conduction study (NCS) : evidence of a motor neuronopathy with intact sensory nerve conductions.
- MRI: **most helpful test.** spinal cord lesions largely restricted to the gray matter and spanning ≥1 spinal segment. Lesions tend to be longitudinally extensive. The cervical cord is the most commonly affected.



ACUTE FLACCID MYELITIS

- **Treatment:**
- Supportive treatment (securing the airway, treating autonomic dysfunction, managing pain, preventing the complications of acute immobility, and beginning early rehabilitation). Many give steroids, IVIG or Plasma exchange but not proven to be helpful.
- **Outcome:**
- Fewer than 10 % achieve full recovery, most end with residual deficits.

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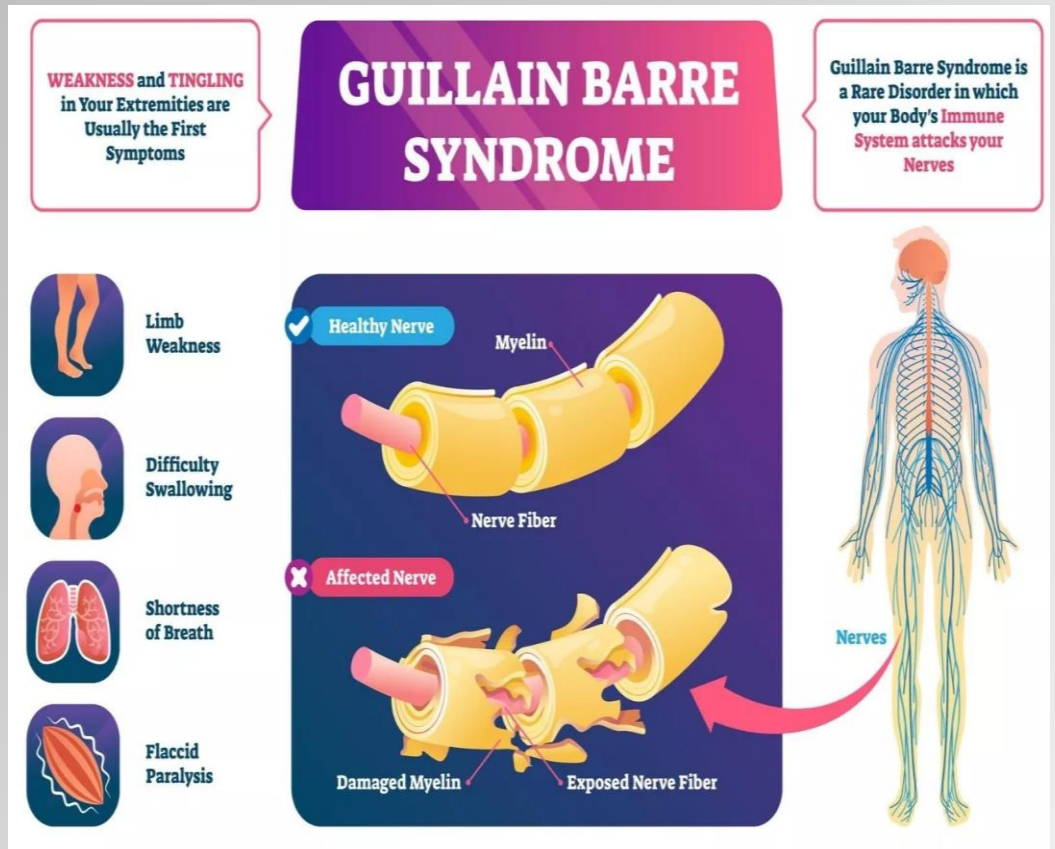
GUILLAIN BARRE SYNDROME (GBS)

- It is an autoimmune-mediated inflammatory disease of the peripheral nerves.
- It happens when a trigger evokes an immune response, which cross-reacts with peripheral nerve components leading to polyneuropathy.
- Common triggers: infections (most common is campylobacter, also CMV, EBV, and Mycoplasma), immunizations(e.g. influenza vaccine), surgery, or trauma.
- Typical age in children is 4-8 years. No seasonal predilection.

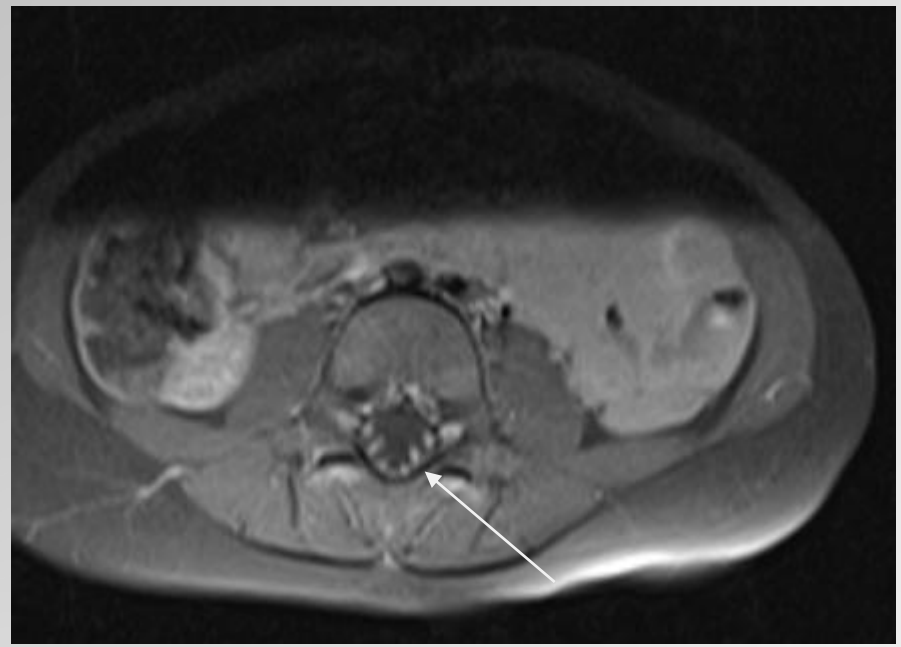
GUILLAIN BARRE SYNDROME (GBS)

- The main type of GBS is AIDP (acute inflammatory demyelinating polyneuropathy). Other types include axonal motor neuropathy (AMAN) and variants that affect cranial nerves (Miller Fisher).
- The classic presentation of AIDP begins with paresthesia in the toes and fingertips followed by lower extremity symmetric weakness that may ascend over hours to days to involve the arms and, in severe cases, the muscles of respiration.
- Pain is a prominent symptom in young kids and is more frequent compared to adults.
- Disease severity in pediatric patients is the same as in adult patients.
- Exam: flaccid paralysis with decreased or absent deep tendon reflexes.



GUILLAIN BARRE SYNDROME (GBS)

- **Investigations:**
- Antibodies: GM1, GM1b, GD1a in AIDP. GQ1b in Miller Fisher
- CSF: cyto-albuminologic dissociation.
- NCS: conduction block in AIDP.
- MRI with contrast: nerve root enhancement.



GUILLAIN BARRE SYNDROME (GBS)

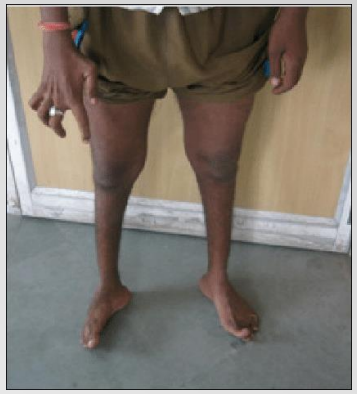
- **Treatment:** Supportive. IVIG or plasma exchange. Steroids generally not helpful and may be harmful.
- **Outcome:**
- The outcome is more favorable in children than in adults.
- Deaths are relatively rare, especially if the disorder is diagnosed and treated early.
- The recovery period is long, often weeks to months, with a median estimated recovery time of 6–12 months.
- Recurrence in 5% of cases.

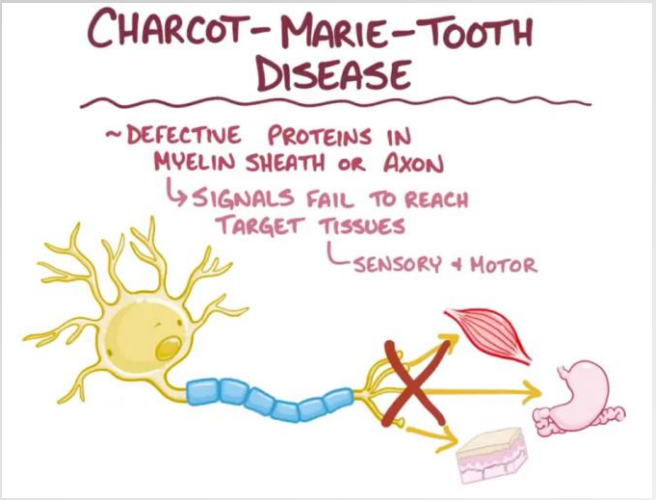
OUTLINE

- Charcot Marie Tooth
- Infantile Botulism
- Myasthenia Gravis
- Duchenne Muscular Dystrophy

CHARCOT MARIE TOOTH (CMT)

- Hereditary.
- Distal weakness. Decreased sensation. Absent deep tendon reflexes.
- High arched foot. Hammer toes . Distal muscle atrophy (inverted Champagne sign).
- Nerve conduction studies (NCS): to identify delayed motor and sensory nerve conduction velocities seen in neuropathy.
- Electromyography (EMG): to differentiate from myopathies.
- DNA testing: More than half of all cases of CMT are caused by a duplication of the PMP22 gene on chromosome 17.



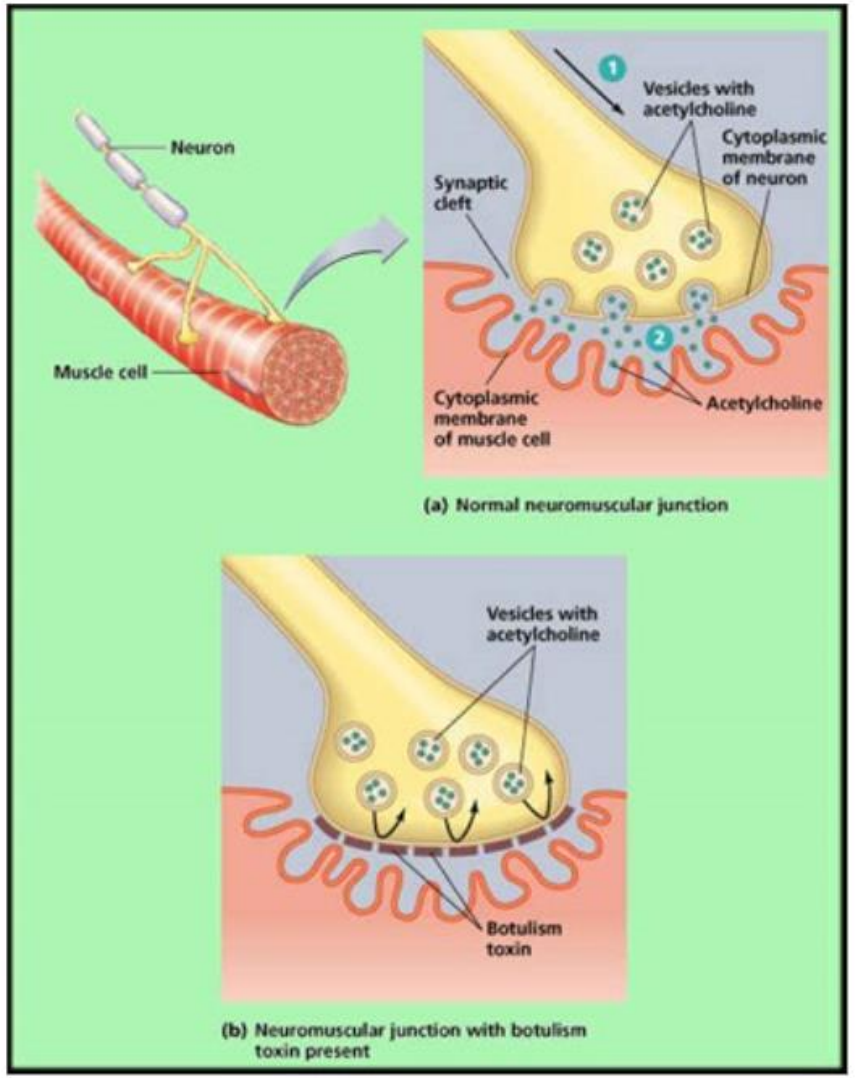


INFANTILE BOTULISM

- It occurs when *C. botulinum* spores are ingested, colonize the host's GI tract, and release toxin produced in vivo.
- It is classically associated with the ingestion of raw honey, but this is not the most common cause. Most cases result from ingestion of environmental dust and soil-containing spores.
- Age: 1 wk to 1 yr. Mostly 2-8 months of age.
- History: descending paralysis. Muscles innervated by the cranial nerves are affected first, followed by those of the trunk, extremities, and diaphragm.

Pathogenesis

- The botulinum toxin is absorbed into the bloodstream;
- It leaves the circulatory system at the point where a neuron joins a muscle;
- The toxin prevents the fusion of synaptic vesicles of acetylcholine
- There is no release of acetylcholine at the neuromuscular junction, with consequent paralysis of the muscle fiber.



Pre synaptic

INFANTILE BOTULISM

- Infants typically present with constipation and poor feeding, followed by progressive hypotonia and weakness, with loss of deep tendon reflexes.
- Cranial nerve dysfunction is manifested by decreased gag and suck, diminished range of eye movement, pupillary paralysis, and ptosis.
- Autonomic signs include decreased tearing and salivation, fluctuating heart rate and blood pressure, and flushed skin. may present with or progress to life-threatening respiratory failure requiring ventilator support.
- Diagnosis: mostly clinical. It is supported by the isolation of *C. botulinum* spores from the stool and is confirmed by the identification of botulinum toxin in stool samples. May be difficult to get stool samples with constipation, and the test results take time. May consider NCS.
- Treatment: supportive. Botulism immune globulin intravenous (BIG-IV or BabyBIG), a human-derived botulinum antitoxin should be administered as early as possible.

Infant Botulism

Signs and Symptoms

- Poor feeding (weak sucking)
- Weak gag
- Weak cry
- Decreased movement
- Appearing lethargic
- Flat, blunted facial expression
- Trouble swallowing
- Excessive drooling
- Muscle weakness
- Breathing problems
- Ptosis (Drooping eyelids)
- Poor head control
- Decreased anal sphincter tone
- Decreased deep tendon reflexes

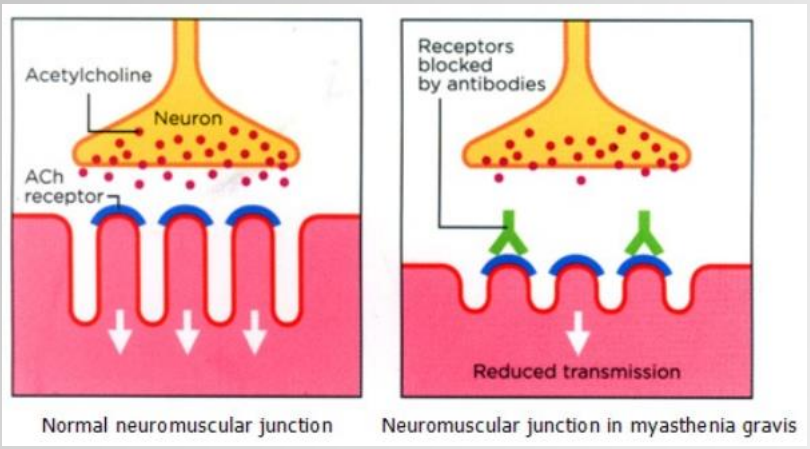
Treatment and Recovery

- New drug: BabyBIG®, Botulism Immune Globulin Intravenous (Human) (BIG-IV)
- Drastically reduces lethargy, IV feeding and overall hospital stay
- With early detection, proper treatment, no long term effects observed

MYASTHENIA GRAVIS (MG)

- It is an antibody-mediated autoimmune disease that affects the postsynaptic neuromuscular junction.
- Typically presents with a slowly progressive course. Most common symptoms include ptosis and diplopia. These symptoms are generally exacerbated by activity and relieved by rest (fatigability).
- **Diagnosis:** ice pack test, edrophonium test: no longer used. Antibody tests: Anti AChR, and anti MuSK antibodies. May consider NCS/EMG.
- **Treatment**: supportive, pyridostigmine, immunotherapy, thymectomy.

Post synaptic

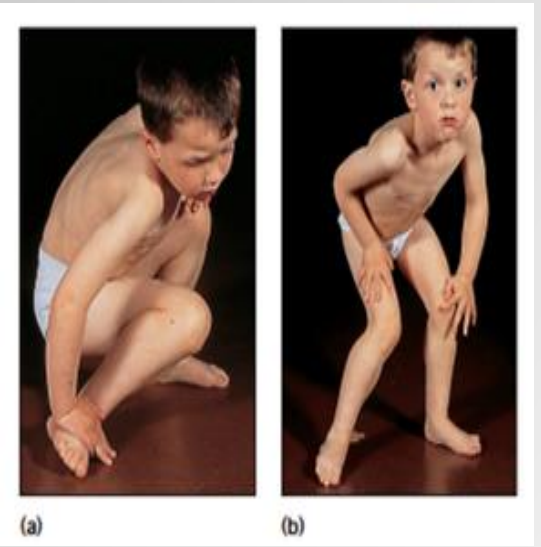


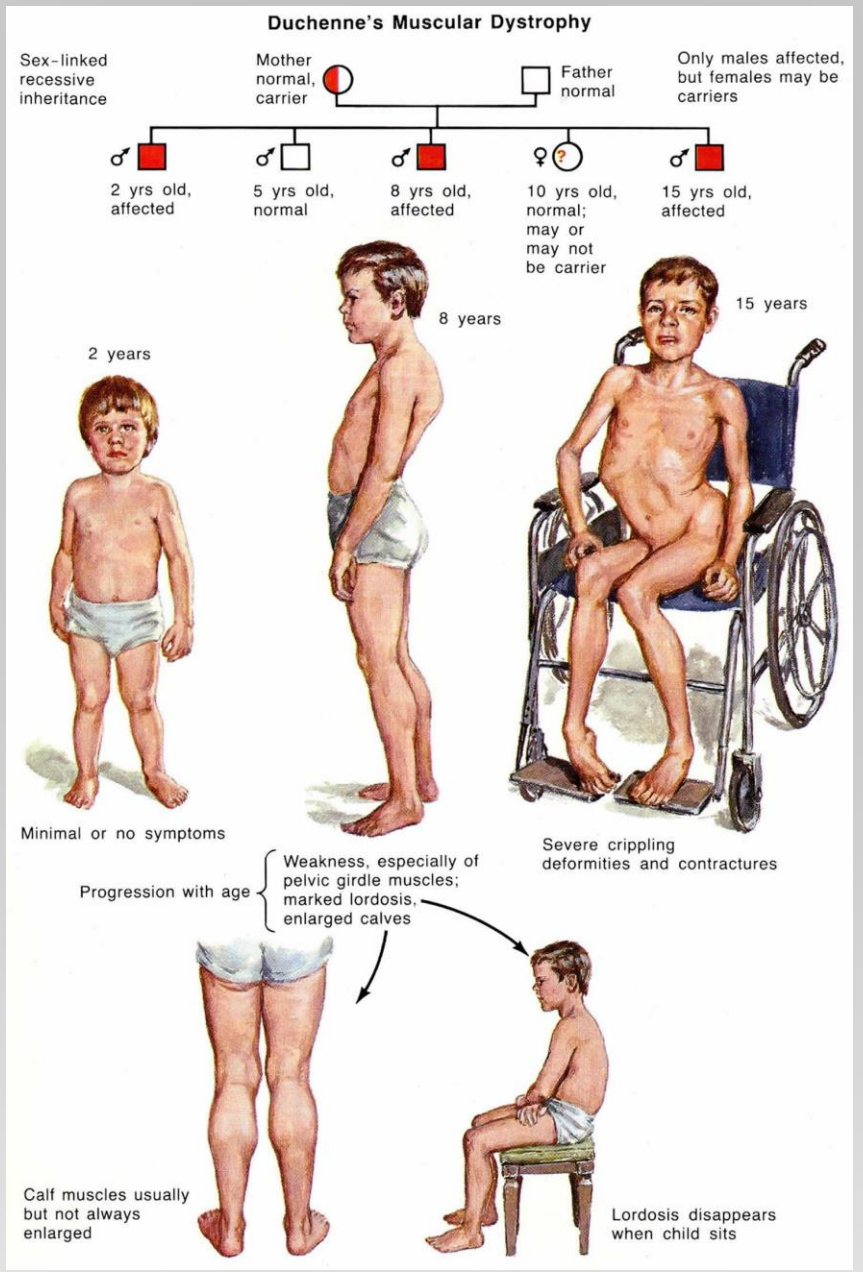
MYASTHENIA GRAVIS

- **Transient neonatal myasthenia** affects 10-15% of babies born to mothers with myasthenia gravis. It can lead to weakness, dysphagia, and occasionally, respiratory distress or failure.
- **Congenital Myasthenia** is not autoimmune mediated, genetic disease affecting the channels.

DUCHENE MUSCULAR DYSTROPHY (DMD)

- Caused by a defective *DMD* gene located on the X chromosome that is responsible for the production of dystrophin. (X-linked recessive).
- It leads to progressive proximal muscle weakness.
- Other symptoms: cardiomyopathy, cognitive dysfunction.
- Exam: +ve Gower's sign. Pseudohypertrophy of the calf muscle.
- Work up :
  - Serum CK: elevated in Duchenne and Becker muscular dystrophy.
  - Muscle biopsy: confirms the diagnosis, no longer used.
  - DNA testing – to identify the pathogenic mutation.
- Treatment: supportive. Steroids. Gene therapy (converts DMD to BMD)




Duchenne's Muscular Dystrophy
Sex-linked recessive inheritance
Mother normal, carrier
Father normal
Only males affected, but females may be carriers
2 yrs old, affected
5 yrs old, normal
8 yrs old, affected
10 yrs old, normal; may or may not be carrier
15 yrs old, affected
2 years
8 years
15 years
Minimal or no symptoms
Progression with age
Weakness, especially of pelvic girdle muscles; marked lordosis, enlarged calves
Severe crippling deformities and contractures
Calf muscles usually but not always enlarged
Lordosis disappears when child sits

Amal Abu Libdeh, MD