Muscular dystrophy (MD)

📢: MD refers to a group of nine inherited progressive myopathic (progressive weakness) disorders resulting from defects in a number of genes required for normal muscle function. I'll mention duchenne, becker and myotonic dystrophy (DMD, BMD and MD).

Duchenne & Becker

- Duchenne (DMD) & Becker (BMD) both R X-linked recessive so only male R affected.[1]
- **Pathophysiology**: Mutations of the dystrophin protein[2], complete in DMD and partial in BMD.[3] (It's complete in DMD; which makes it logical that DMD is more severe, has earlier onset, causes more/earlier impairment and has faster progression).

🧠 **D**uchenne is caused by **D**eleted **D**ystrophin ❗

- **Clinical features**:[4]
  - Paresis and atrophy (starting in the proximal lower limbs, later spreading to the upper body and distal areas).
  - Waddling gait (bilateral Trendelenburg's sign), hypo-tonia/reflexia, calf pseudohypertrophy.
  - **Gower sign +ve[5].**
  - Cardiac and respiratory muscle involvement: Dilated cardiomyopathy (common cause of death), arrhythmias, respiratory insufficiency.

- **D**x:
  - Blood tests: ↑↑ **creatine kinase**.
  - Genetic analysis (confirmatory): detect dystrophin gene mutation.
  - Muscle biopsy: Only performed if genetic analysis is inconclusive.[6]

- **R**x: currently there is no curative treatment for muscular dystrophies !
  - Medical therapy: **Glucocorticoids** (e.g., prednisone) for **DMD**, also for BMD although their efficacy is low.
  - Supportive therapy: Physiotherapy, orthopedic assistive devices (wheelchairs, walkers), psychological support, ventilation support.

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[1] DMD is more severe, with disease onset typically occurring at two to three years of age. BMD usually does not become evident before the age of 15. DMD progresses rapidly and typically leads to ambulatory inability by age 12. The life expectancy for patients with DMD is approx. 30 years, whereas patients with BMD have a longer life expectancy (hence DMD early onset and rapid progression).
[2] A sarcolemmal protein in **skeletal and cardiac** muscles that anchors the cytoskeleton of a muscular cell to the extracellular matrix by connecting cytoskeletal actin filaments to membrane-bound dystroglycan that is, in turn, connected to extracellular laminin.
[3] Mutations and subsequent alterations of the dystrophin protein → partial (BMD) or almost complete impairment (DMD) of the protein → disturbance of numerous cellular signaling pathways → necrosis of affected muscle cells and subsequent replacement with connective and fat tissue → muscle appears larger ("pseudohypertrophy")
[4] Sx R identical for both. BMD has slower progression, milder Sx and more heart involvement. DMD Onset before the age of 5.
[5] To stand up, the patient supports himself on his thighs and uses the hands to essentially "walk" up the body until reaching a standing position. It is a classic sign in DMD but also occurs in e.g., BMD, dermatomyositis.
[6] Muscle fibers diameter changes, necrosis & replacement with adipose tissue. DMD (absent dystrophin), BMD (reduced dystrophin).

Myotonic dystrophy[7]

- **Types**:
  1. Myotonic dystrophy type I (**DM I**): congenital, juvenile, or adult onset. (more severe).
  2. Myotonic dystrophy type II (**DM II**): usually adult onset.

DM I[8] (Curschmann-Steinert disease)	**DM II** (proximal myotonic myopathy)
• Skeletal muscle weakness and myotonia (delayed muscle relaxation following normal muscle contraction). • Muscle pain, arrhythmias, cataracts. • Testicular atrophy or features of ovarian insufficiency (i.e., infertility). • Hypogammaglobulinemia, features of insulin resistance, frontal balding, cognitive impairment.	
• Most common in the distal sections of extremities: face (**V-shaped upper lip**), neck, forearm, foot dorsiflexor (**bilateral drop foot**), intrinsic muscles of the hand (compromised finger dexterity). • **Myopathic facies**: Long, narrow face, hollowed cheeks, and high arched palate, ptosis, SCM muscle wasting. • Clinical myotonia: Classically manifests as difficulty releasing a handshake. • Respiratory involvement, dysphagia, dysarthria, IBS Sx, impaired sleep, daytime somnolence are common.	• Most common in the proximal muscles: neck flexors, hip flexors, elbow flexors, finger flexors • **Mild** clinical myotonia • Uncommon symptoms: respiratory muscle involvement, dysphagia, dysarthria, irritable bowel-like symptoms (e.g., abdominal pain, bloating), impaired sleep, daytime somnolence are uncommon.

Dx: Clinical (characteristic presentation & +ve FHx) + Genetic.

- **Genetic diagnostics** (confirmatory): detection of trinucleotide repeat expansion mutation in leukocytes.[9]
- Electromyography (EMG): identifies myotonia (if uncertain).[10]
- Biopsy: to distinguish between an inflammatory and a metabolic cause of the myopathy (if uncertain)
- Other supportive tests.[11]

Rx: Incurable !

- Symptomatic treatment (analgesia, physiotherapy, walking aids, pacemaker, medical therapy for myotonia).
- Regular monitoring (i.e., of respiratory compromise, dysphagia).

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[7] **Autosomal dominant** multisystem disorders characterized by skeletal muscle weakness and myotonia (abnormally slow or delayed muscle relaxation following a normal muscle contraction), cardiac conduction abnormalities, cataracts, and others.

[8] 🧠 MD-I is caused by a **CTG** nucleotide repeat expansion and results in **C**ataracts, **T**oupee (premature hair loss in men), and **G**onadal atrophy ❗

[9] Type 1 (CTG trinucleotide repeat expansion of DMPK gene). Type 2 (CCTG tetranucleotide repeat expansion of ZNF9 gene "CNBP gene")

[10] Repetitive discharges that wax and wane in both frequency and amplitude (crescendo-decrescendo sound). Useful in cases in which the diagnosis is ambiguous or clinical symptoms of myotonia are absent.

[11] **Labs** (↑ CK, IgG and IgM hypogammaglobulinemia, ↑ FSH and ↓/↔ testosterone). **ECG** (to exclude cardiac arrhythmias and other abnormalities). **MRI** (signs of global atrophy → MD I).

Spinal muscular atrophy (SMA)[12]

- Neuromuscular disorder characterized by a degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem → hypotonia and progressive muscle weakness.
- *Infant in a frog-leg position with subdiaphragmatic retractions and absent reflexes* → SMA1.

	Type I (Werdnig-Hoffman)	**Type II**	**Type III**	**Type IV**
	Severe	**Intermediate**	**Mild**	
Onset	**0-6** Months	**7-18** Months	**>18** months	**>5** Years
Features	1. Severe muscle weakness and hypotonia.[13] 2. Diminished or absent deep tendon reflexes (sensation is preserved). 3. Severe bulbar palsy.[14]	1. Delayed motor milestones. 2. Poor weight gain. 3. Fine hand tremors, weak cough. 4. Joint contractures, kyphosis, and/or scoliosis.	1. Variable degree of muscle weakness. 2. Cramps, muscle aches. 3. Joint pain.	
Motor milestones	Never sit or attain head control.	Able to sit independently, but cannot stand without support.	Able to stand and walk independently.	
Prognosis	Life expectancy (< 2 years)	Life expectancy (> 2 years)	Near normal life expectancy	

🧠 Type **I** → non-sitters, type **II** → sitters, type **III** → walkers ❗

Dx:
- **Genetic** testing: best initial and confirmatory test (SMN gene).
- Further tests: Laboratory tests (normal or mildly elevated creatine kinase), EMG (abnormal spontaneous activity with fibrillations and positive sharp waves "rarified interference pattern"), Muscle biopsy (atrophy of groups of motor units interspersed with normal or hypertrophied motor units).

Rx
- Definitive therapy: **intrathecal nusinersen**.
- Supportive therapy: Respiratory support, Nutritional support (feeding tubes), Physical rehabilitation, Orthotics to prevent joint and spine deformities (joint contractures and scoliosis).

DDx

1. Certain viral infections (polio, coxsackievirus, echovirus, West Nile virus) → much more acute onset of flaccid paralysis, ascending paralysis (i.e., starts distally). / **2.** Hypotonic cerebral palsy → non-progressive weakness.
3. Muscular dystrophies → ↑↑ creatine kinase, characteristic findings on muscle biopsy.
4. Rare juvenile form of amyotrophic lateral sclerosis → predominantly bulbar weakness with minimal involvement of anterior horn cells. / **5.** Motor neuron degeneration → associated with severe arthrogryposis.

[12] Motor disease that only involves the LMNs (spinal ± bulbar motor neurons) → muscle weakness, hypotonia, bulbar Sx; preserved sensations. Motor neurons of cranial nerves III, IV, & VI, & sacral motor neurons not affected → preserved eye movement and continence.
[13] **Symmetrical** involvement of **proximal** muscles, mostly of the **lower** extremities. Intercostal muscle weakness → paradoxical breathing (The abdomen protrudes while the chest wall collapses, resulting in a bell-shaped trunk).
[14] **1/**Respiratory failure, weak cry & cough. **2/**Tongue atrophy & fasciculations. **3/**Inability to swallow → difficulty feeding, drooling, ↑ risk of aspiration.

Guillain-Barre syndrome (GBS)

- Acute postinfectious polyneuropathy characterized by symmetric and ascending flaccid paralysis (prototype “AIDP”).
- **Etiology**: majority of patients experience Sx of an URTI or GIT (diarrhea) infection 2-4 weeks prior to onset of GBS.[15]
- **Pathophysiology**: Postinfectious autoimmune reaction that generates cross-reactive antibodies attacks the host's own axonal antigens, resulting in inflammatory and demyelinating polyneuropathy.(molecular mimicry).[16]

- **Clinical features**:[17] [18]

  A. Initial symptoms: back and limb pain, esp. paresthesias affecting distal extremities (fingertips, toes).

  B. Advanced symptoms:
  - Ascending paralysis: Bilateral flaccid paralysis spreads from lower to upper limbs in a “stocking-glove” distribution.
    - Cranial nerve involvement: frequently bilateral facial nerve involvement (facial diplegia).
    - Landry paralysis: involvement of the respiratory muscles.
  - Reduced or absent muscle reflexes.
  - Peripheral, symmetric paresthesias in the hands and feet.
  - Autonomic dysfunction[19]: Cardiovascular (arrhythmia), voiding dysfunction, and/or intestinal dysfunction.

Subtype[20]	Details
Acute inflammatory demyelinating polyneuropathy (AIDP)	• Acute variant of Guillain-Barré syndrome. Predominant subtype. • Associated with **Campylobacter enteritis** and CMV. • Autoantibodies against various antigens. • Ascending paralysis, autonomic neuropathy, CN defects and pain, clinical nadir ~4 weeks.
Miller fisher syndrome	• **External ophthalmoplegia**, **ataxia**, and **muscle weakness** with **areflexia**. [21] • Serological detection of autoantibodies (against ganglioside GQ1b, GT1a) confirms Dx. • Brainstem auditory evoked potentials demonstrate peripheral & central conduction defects.

[15] Pathogens: bacteria (**Campylobacter jejuni**, Mycoplasma pneumoniae), viruses (**CMV**, Epstein-Barr virus, HIV, influenza). Campylobacter enteritis is the most common disease associated with GBS. Cytomegalovirus is the most common virus.
[16] Infection triggers humoral response → autoantibodies against gangliosides or other unknown antigens of peripheral Schwann cells → immune-mediated segmental demyelination → axonal degeneration.
[17] The classic presentation of GBS begins with **paresthesia** in the toes and fingertips followed by lower extremity **symmetric** or modestly asymmetric weakness that may **ascend** over hours to days to involve the arms and, in severe cases, the muscles of respiration. The predominant symptoms of GBS at presentation in children are **pain** and **gait difficulty**. In preschool-aged children, the most common symptoms are **refusal to walk** and pain in the legs.
[18] PEx typically reveals symmetric weakness w/ diminished/absent reflexes & gait abnormalities. Sensory Sx are usually "positive" (pain or paresthesia, reflecting nerve irritability) rather than "negative" (eg, loss of sensation). Early Sx may be atypical (difficult to Dx). Some cases present with initial proximal weakness, or less common findings such as sphincter disturbances, raising concerns about a possible spinal cord lesion.
[19] Orthostatic hypotension, transient or persistent hypertension, paralytic ileus, bladder dysfunction, abnormal sweating.
[20] Historically, GBS was considered a single disorder, but it is now known to be a heterogeneous syndrome with several variant forms. Most often, GBS presents as an acute monophasic paralyzing illness provoked by a preceding infection (AIDP). In addition to the demyelinating form, which is the most common type, axonal forms of GBS are also well-recognized (acute motor axonal neuropathy, acute sensorimotor axonal neuropathy, Miller Fisher syndrome).
[21] Incomplete forms include acute ophthalmoplegia without ataxia, and acute ataxic neuropathy without ophthalmoplegia.

Dx:

- **CSF**: Albuminocytologic dissociation: elevated protein levels and normal cell counts (WBCs is normal).[22]
- **Electroneurography**: reduced nerve conduction velocity (NCV) due to demyelination : increased F-wave latency.[23]
- **Serology**:
  - To identify potential pathogens (e.g., Campylobacter jejuni).
  - Detection of antibodies (IgG) directed against gangliosides (e.g., GQ1b, anti-GM1 antibodies).

Rx:

- Supportive management.[24]
- **IVIG** (High dose of intravenous immunoglobulins).
- Plasmapheresis (plasma exchange).[25]

Poliomyelitis

- Infectious disabling and life-threatening disease caused by the poliovirus.
- **Pathophysiology**: Virus replicates in GI following oral ingestion → enters the bloodstream → potential invasion of the grey matter of the spinal cord (particularly anterior horn cells) → myelitis (hyporeflexia, hypotonia, weakness).

Clinical features: Over 90% are asymptomatic - clinical forms:

1. Poliomyelitis **without CNS** involvement (abortive poliomyelitis).[26]
2. Poliomyelitis **with CNS** involvement:
   A. Nonparalytic poliomyelitis (aseptic meningitic form).[27] **B. Paralytic** poliomyelitis.[28]

Complications:

- Ascending paralysis with diaphragmatic involvement → respiratory failure.
- Bulbar form with brain stem involvement (rare): damage to the cerebral or autonomic nerve centers (cranial nerves and respiratory center) → central respiratory paralysis.

Post polio syndrome: Most frequent complication, occurs decades after infection manifests with progressive muscle weakness and pain, even in areas that were not affected by the initial infection.

Dx: **PCR** (Best) → **Amplification** of poliovirus RNA from **CSF**[29].
Rx: Pain relief, **Mechanical ventilation** if needed (respiratory muscles involvement), and close monitoring of BP and respiratory function (Polio with bulbar involvement can cause autonomic dysfunction).
Prevention: Children receive 4 doses of IPV (inactivated polio vaccine), at 2, 4 and 6–18 months, followed by a booster dose at 4–6 years.

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[22] Breakdown of the blood-nerve barrier at the dural attachment allows transudation of plasma proteins into the cerebrospinal fluid.
[23] Electrodiagnostic studies are the most specific and sensitive tests for diagnosis of GBS, and establish the underlying pathophysiology as either **demyelinating** (prolonged latency and slow conduction velocity) or **axonal** (lower amplitudes).
[24] Monitor cardiac & resp function. ICU Tx and intubation may be indicated. Prevent decubitus and/or thrombosis (esp. PE).
[25] In children (only recommended in rapidly progressing or severe disease), In adults (equivalent outcome as IVIG).
[26] Nonspecific symptoms: gastroenteritis, fever, nausea, sore throat, myalgia, and headaches for 1–3 days. Complete recovery without complications or transition to poliomyelitis with CNS involvement.
[27] Begins several days following abortive poliomyelitis (often temporary, symptom-free interval). Fever, neck stiffness, headache, vomiting, muscle pain. Neck muscle weakness (head drops back). **No paresis**!
[28] Occurs 2–3 days following the meningitic form after a brief symptom-free interval. Fever, severe back, neck, and muscle pain. Asymmetric flaccid paralysis# worsens over hours to days, diminished deep tendon reflexes.
[29] CSF fluid will also show high protein levels and pleocytosis with either neutrophils (early infection) or lymphocytes (late).

Myasthenia gravis (MG)

- Autoimmune[30] neuromuscular disease → generalized muscle weakness.
- Associated with: Thymoma[31], females, other autoimmune diseases (hashimoto, RA, SLE, sarcoidosis).
- Main clinical forms: Ocular MG, generalized MG.[32]
- Pathophysiology:
  - Thymus involvement: It is hypothesized that the thymus is involved in the pathogenesis of MG.[33]
  - AChR antibodies: Sero (+ve/-ve) against AChR/MuSK.[34]

- Clinical course[35]: Sx worsen w/ muscle use and improve with rest. Sometimes associated w/ exacerbating factors.[36]
- **Clinical manifestations:**
  1. **Eye** muscle weakness (most common initial Sx) → **Ptosis**, Diplopia, Blurred vision.
  2. **Bulbar** muscle weakness → dysarthria, dysphagia, and fatigable chewing (**infant feeding difficulties**).
  3. **Proximal** limb weakness → Rising from chair, climbing stairs, brushing hair, **floppy infant w/ poor head control**.
  4. Weakness of **respiratory** muscles → respiratory insufficiency.

- **Dx**[37]:
  - **AChR antibody** test (most specific test).[38]
  - **Electrophysiology**: A decremental response following repetitive nerve stimulation & abnormal single fiber EMG.
  - Chest CT: always indicated in newly diagnosed MG patients to rule out thymoma.
  - Edrophonium test (Tensilon test): Rapid improvement after administration of a short-acting acetylcholinesterase inhibitor. High false positive rate.

- **Rx**[39]:
  - First line: **cholinesterase inhibitors** (pyridostigmine) provides symptomatic relief.
  - Supplemental immunosuppressants (Glucocorticoids)[40]: if Sx persists despite anticholinesterase treatment.
  - Rapid immunomodulating therapies (in cases of myasthenic crisis): Plasmapheresis, IVIG.
  - Thymectomy.[41]

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[30] Autoimmune: autoreactive ab directed against postsynaptic AChR or receptor-associated proteins (impairing neuromuscular transmission). In rare cases, can be caused by graft-versus-host reaction after allogeneic stem cell transplantation (especially in children).
[31] The most common primary tumor in the anterior mediastinum, 10-12% of pts. Thymic hyperplasia in 60-70% of patients.
[32] **1.** Ocular myasthenia (only the extraocular and/or eyelid muscles), **2.** Generalized myasthenia: all skeletal muscles may be involved; especially the ocular, bulbar, limb, and respiratory muscles.
[33] Muscle-like (myoid) cells in the thymus express AChR → thymic T cells target myoid cells → AChR Abs production → Abs target postsynaptic AChRs of normal muscle cells, competing with acetylcholine (ACh) → impaired signal transduction in the NMJ resulting in skeletal muscle weakness & fatigue, and AChR decay and reduced receptor density on the postsynaptic membrane.
[34] Seropositive MG (85% of cases): positive for Abs against AChR, or against muscle specific tyrosine kinase (MuSK). Seronegative MG (15% of cases): negative assays for both AChR-Ab and MuSK-Ab.
[35] The most common initial Sx are ptosis and/or diplopia due to ocular muscle weakness, with the disease usually progressing to generalized weakness within two years. At that point, patients have difficulties standing up, climbing stairs, and possibly even swallowing and/or chewing.
[36] Meds (muscle relaxants, BB, benzos, **aminoglycosides**, antipsychotics, TCAs, d-penicillamine), stress, infection, pregnancy. Smaller muscles responsible for fine movements (eye muscles) tend to be affected 1st, while larger muscles become affected later on.
[37] MG is diagnosed according to Hx, PEx, Abs testing, and EMG evaluation. All pts should be screened for thymomas via CT.
[38] 85% of pts with generalized MG have ab. 100% of pts with thymoma have ab. Other associated antibodies: anti-MuSK.
[39] The treatment of choice consists of acetylcholinesterase inhibitors, possibly in combination with immunosuppressive drugs if Sx persist. Acute exacerbations, as seen in myasthenic crisis, should be treated with either IV immunoglobulins or plasma exchange.
[40] Alternatives: azathioprine, cyclosporine, mycophenolate mofetil.
[41] Can be beneficial even if a thymoma is not present. Not for patients with MuSK antibody-associated MG without a thymoma.

Cerebral palsy (CP)

- A heterogenous group of disorders affecting the muscle tone and the development of movement and posture.[42]
- **Etiology**:
  - Idiopathic (most cases).
  - Risk factors: Preterm birth and low birth weight (most important risk factors), TORCH infection, perinatal asphyxia, intracranial hemorrhage, structural abnormality of the brain, neonatal seizures, kernicterus, Postnatal infection (e.g., meningitis, encephalitis).

Classification:[43]

A. Spastic CP: spastic paresis of one or more limbs (75% of cases).

B. Non-spastic CP:

a. Dyskinetic: abnormal involuntary movements (choreoathetoid, dystonic).

b. Ataxic: intention tremor, lack of balance and coordination.

Clinical features: Pts may present W/ mixed types of cerebral palsy (e.g., combination of spastic and athetoid CP).

- **All types**: Pts do not reach certain milestones, intellectual disability, seizure disorder, joint contractures, ADHD.

- **Spastic** type:
  - ↑ Muscle tone in one or more limbs, ↑ DTRs. Persistence of primitive reflexes (e.g., positive Babinski sign).
  - Toe walking or equinus deformity, muscle weakness and/or atrophy, scissor gait (as a result of spastic paraplegia of the hip adductors), hip dislocation, scoliosis, hearing or vision impairment.
- **Non-spastic** type: Abnormal involuntary movements that worsen with stress and disappear with sleep: chorea, athetosis, dystonia, ataxia. Dysarthria and dysphagia (pseudobulbar involvement).

Dx: mainly based on the clinical picture !

- Cranial US (early neonatal period): intracerebral hemorrhage and/or hypoxic-ischemic injury, structural abnormalities.
- MRI (in older infants): to detect causative lesion (e.g., periventricular leukomalacia, congenital malformation, intracranial hemorrhage).

Rx: There is no curative therapy !

- Antispasmodics (e.g., botulinum toxin, baclofen, dantrolene, benzodiazepines).
- Physical therapy, surgery (e.g., to treat scoliosis or relieve joint contractures).
- Bracing to prevent contractures, speech therapy for dysarthria, nutritional support for dysphagia, special tuition for intellectual disability, social and psychological support.

[42] CP results from a non-progressive damage to the brain in utero or during infantile development up to the age of 3 years. Depending on the affected brain area, spastic, ataxic, or dyskinetic cerebral palsy develops.

[43] Spastic → Caused by damage to the cortex/pyramidal tract. Non-spastic → Caused by damage to the extrapyramidal tracts (e.g., basal ganglia, cerebellum).

Neural tube defects (NTDs)

- A group of congenital malformations of the brain and spinal cord.[44]
- They develop between the 3rd and 4th week of pregnancy; the neural tube in the embryo closes during this time.
- Associated maternal conditions: DM, obesity, fever/hyperthermia during first trimester.

Subtypes

A. Spina bifida → primarily in the **lower** lumbar to the sacral region.

1. **Occulta**: Failure of one or more vertebrae to close; the spinal cord, meninges, and overlying skin remains **intact**.
   Sx: Usually **asymptomatic**; possibly visible dimple, collection of fat, or patch of hair on the skin above the defect.

2. **Cystica**: Failure of one or more vertebrae to close completely; the meninges (meningocele) and potentially the spinal cord (myelomeningocele) **may protrude** through the gap.[45]
   Sx: Symptoms of spinal cord dysfunction (varying degrees of motor loss, possible flaccid paralysis. Sensory deficits, Bladder and bowel dysfunction.)[46]

B. Cranial defects: cranial cleft formation with involvement of the skull and brain. Location is variable.

1. Acrania: absent skull bones.
2. Anencephaly: variable presentations of diminished cranium and forebrain, as well as cerebellum.
3. Encephalocele: protrusion of the brain via an opening in the skull.
4. Cranial meningocele: protrusion of meninges through parietal foramina or abnormal bony openings of the skull.

Sx: malformations and neurological deficits that vary in severity; in severe cases always lethal.

C. Congenital dermal sinus: mainly lumbar or lumbosacral fistulae; extend from the surface of the skin to the spinal canal and frequently end in a dermoid or epidermoid cyst.

Dx:

- Prenatal screening:[47]
  - Elevated levels of alpha-fetoprotein (AFP) in amniotic fluid at 13–15 weeks' gestation.
  - Fetal ultrasonography at 20 weeks' gestation.
- CT scans and cranial ultrasonography (in infants) to monitor possible hydrocephalus.
- MRI for assessment of spinal cord malformations.

Rx:

- The baby is usually delivered by CS. Placement of a VP shunt in cases of hydrocephalus.
- Prophylactic administration of broad-spectrum antibiotics.
- Surgical closure within 72 hours after birth ; close monitoring and possibly elective surgery for closed defects.

Prevention: **Folic acid** supplementation.[48]

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[44] Improper closure of the neural plate in the embryo (due to folic acid deficiency) resulting in malformations of the CNS, spine, & cranium.
[45] Beneath the skin, the cystic mass is comprised of adipose tissue, connective tissue, ependymal cells, nerve cells, and glial tissue.
[46] Further Sx: Developmental delays, cognitive impairment, progressive neurological symptoms. Skeletal malformations (esp. of the spine and lower extremities), joint contractures, back pain. Hydrocephalus.
[47] AFP: If AFP levels are elevated but US is inconclusive, the diagnosis can also be confirmed through elevated levels of acetylcholinesterase in the amniotic fluid. US → Shows concavity of the frontal bones, ventriculomegaly, and a Chiari II malformation.
[48] 400–800 µg/day at least 4 weeks prior to pregnancy. Intake should continue through the first trimester. Women who have had a child with an NTD or have one themselves should take 4 mg/day starting 4 weeks prior to trying to conceive.

DDx

Tethered cord syndrome

Spinal cord abnormal stretching, caused by adhesions/obstructions that tether the cord to the base of the spinal canal.

Etiology: Meningeal adhesions, Terminal filament adhesions or thickening, Lipoma, dermoid cysts, tumors.

Sx:

- (Motion-dependent) back pain. skin lesion on lower back (e.g., discoloration, nevi, hemangioma).
- Sensory and motor deficits, skeletal malformations (e.g., foot deformities, scoliosis), bladder/bowel dysfunction.
- Children may begin to stumble after learning to walk.

Dx: MRI shows abnormally low position of the conus medullaris.

Rx: removal of structure tethering the spinal cord (e.g., adhesiolysis, resection of lipomas) → prevents progressive deterioration, corrects existing conditions (e.g., urinary retention).

Neurocutaneous syndromes (phakomatoses)

- Are inherited disorders that primarily affect the nervous system and the skin.[49]
- **Pathophysiology**: Mutation of tumor suppressor gene → loss of function → ↑ risk of cancer development.

Clinical features

A. Neurofibromatosis I (NF1):

- Dysfunction of melanocytes → Café au lait spots, lisch nodules, axillary and inguinal freckling (hyperpigmentation).[50]
- Multiple neurofibromas: Soft, painless nodules; typically manifest under or on the skin. Malignant transformation possible. Seizures occurs when the CNS is involved.[51]
- Bone involvement (e.g., cortical thinning, fractures, pseudarthrosis). Scoliosis present in about ⅓ of patients.
- Optic gliomas (i.e., tumor of optic nerve), possibly causing vision abnormalities.
- Associated with pheochromocytoma and Wilms' tumor. Additional findings (short stature, macrocephaly, HTN).

B. Neurofibromatosis II (NF2): Bilateral vestibular schwannomas (aka acoustic neuromas) → ipsilateral tinnitus, hearing loss, vertigo. Multiple cerebral, spinal tumors and meningiomas.

C. Tuberous sclerosis:

- Intellectual disability (caused by brain lesions). Infantile spasms or seizures.
- Skin manifestations:
  - Adenoma sebaceum: reddish nodules in a butterfly appearance around the nose and cheeks (facial angiofibroma); acne-like appearance. ≥ 3 ash-leaf spots, shagreen patch.[52]
  - Small benign tumors:
    - Brain tumors: Hamartomas, giant cell astrocytoma.
    - Cardiac rhabdomyoma (> 50% of patients→ symptoms of congestive heart failure). Ungual fibromas.
    - Renal cysts or renal angiomyolipoma[53]: can present W/ a feeling of abdominal fullness and/or macrohematuria.

[49] Because the brain and the skin have a common ectodermal origin, both organs are often affected simultaneously. These disorders usually follow an autosomal dominant (NFI-II & Tuberous sclerosis) pattern of inheritance and display characteristic skin findings.
[50] Cafe au lait are brownish macules, lisch nodules are pigmented hamartomas on the iris.
[51] Neurofibromas are benign peripheral nerve sheath tumors that originate from neural crest cells and affect the myelinated nerves.
[52] Ash-leaf → hypopigmented/white macules on the trunk and extremities. They are best visualized using black light emitted by a Wood lamp. Shagreen patch → Flesh-colored papules in the lumbosacral region with an orange peel consistency.
[53] Benign renal tumors that arise from perivascular epithelioid cells and consists of blood vessels, smooth muscle, and mature fat cells.

Diagnostics

1. **General:** Take **FHx**, **genetic** testing detects defective gene, **dermatological** exam.
2. **Specific:**

A. NF (I&II):

- **MRI** of the brain and spine with gadolinium enhancement (detection of **neurofibromas**, **meningiomas**).
- **Ophthalmological** exam (optical glioma in NF-**1**). **Auditory** testing (acoustic neuromas in NF-**2**)

B. Tuberous sclerosis:

- **ECG**: cardiac rhabdomyoma (ventricular hypertrophy, arrhythmias). **EEG**: seizure activity.
- **Abdominal MRI**: renal angiomyolipoma. **cCT/MRI**: brain tumors.
- TSC1 mutation on chromosome 9 or TSC2 mutation on chromosome 16 (tumor suppressor genes).[54]

Treatment

★ Since there are no curative treatment options available, treatment of neurocutaneous syndromes focuses on multidisciplinary **symptom control**.

A. NF:

- **Excision/resection** of neurofibromas, meningiomas, acoustic neuromas, and optic gliomas.
- Surgery for kyphoscoliosis in NF1.

B. Tuberous sclerosis:

- **Anticonvulsants** and adrenocorticotropic agents (e.g., prednisone) for seizure control and infantile spasms.
- **Removal of angiofibromas** (laser treatment/electrosurgery).
- **Immunosuppressants** (e.g., mTor inhibitors like sirolimus, everolimus) to treat renal angiomyolipoma and inoperable giant cell astrocytoma.

Not all topics R included in this file; check the objectives provided by the department (seizures lecture is important).
Best wishes 💪😍
Adel Alshihri ^_^

[54] TSC1 gene or TSC2 gene affected; encodes Hamartin or Tuberin protein, respectively. Both function as tumor suppressors.