

Neurocutaneous Disorders

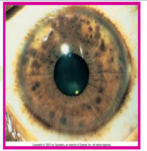
Summary

Neurocutaneous syndromes (phakomatoses) are a diverse class of congenital disorders that affect organs of ectodermal origin, especially the skin, the central nervous system, and the eyes. The disorders most typically included in this class are neurofibromatosis type 1 (NF type 1, von Recklinghausen syndrome), neurofibromatosis type 2 (NF type 2), tuberous sclerosis, von Hippel-Lindau syndrome, Sturge-Weber syndrome, and ataxia telangiectasia. With the exception of Sturge-Weber syndrome, which is caused by a noninherited developmental anomaly of neural crest derivatives, and ataxia telangiectasia, which follows an autosomal recessive inheritance pattern, **neurocutaneous syndromes disorders follow an autosomal dominant inheritance pattern**, although spontaneous mutations are also possible. Characteristic features include neurofibromas, café au lait spots, axillary freckling, pheochromocytoma, optic glioma, and Lisch nodules (NF 1); bilateral vestibular schwannomas, meningiomas, ependymomas, and bilateral cataracts (NF 2); adenoma sebaceum, ash-leaf spots, shagreen patch, giant cell astrocytoma, cardiac rhabdomyoma, and renal angiomyolipoma (tuberous sclerosis); hemangioblastoma, angiomatosis, bilateral renal cell carcinoma, pheochromocytoma (von Hippel-Lindau syndrome); Port-wine stain and leptomeningeal angioma (Sturge-Weber syndrome); spider angioma, lymphoma, leukemia, gastric carcinoma, and ocular telangiectasia (ataxia telangiectasia). Diagnosis is based on clinical findings and is confirmed by genetic testing. Since there is no curative treatment, the management of neurocutaneous syndromes is symptom-oriented.

First: Neurofibromatosis:

Neurofibromatosis type 1 (von Recklinghausen syndrome) [3]

- Multiple **neurofibromas**: benign peripheral nerve sheath tumors that originate from neural crest cells and affect the myelinated nerves.
 - Soft, painless nodules; typically manifest under or on the skin
 - Age of onset: adolescence
 - Malignant transformation possible
- Features due to melanocyte dysfunction:
 - **Café au lait spots**
 - Brown (hyperpigmented), flat macule or patch
 - Age of onset: before 2 years
 - **Lisch nodules**
 - Pigmented iris hamartomas
 - Age of onset: between 5–10 years
 - Axillary and inguinal freckling: age of onset is between 3–5 years
- Seizures and/or focal neurologic signs due to brain lesions (especially meningiomas)
- Intellectual disability
- Bone involvement
 - Scoliosis
 - Sphenoid wing dysplasia
 - Short stature
 - Cortical thinning
 - Fractures
 - Pseudoarthrosis
- Additional findings
 - Associated with certain tumors
 - Pheochromocytoma [4]
 - Nephroblastoma [5]
 - Optic pathway glioma (most commonly involving optic nerve) causing unilateral vision loss, proptosis, or precocious puberty
 - Macrocephaly
 - Hypertension
 - Pulmonary stenosis
- **NF-1** (1 in 3000) diagnosed when 2/7 signs are present:
 1. Six or more **café-au-lait macules** over 5mm in greatest diameter in prepubertal and over 15mm in greatest diameter in postpubertal. present 100% of patients. On trunk and extremities, sparing of the face.
 2. **Axillary or inguinal freckling**: multiple hyperpigmented areas 2-3mm in diameter.
 3. Two or more **iris Lisch nodules**, hamartomas located within the iris, identified by a slit-lamp examination. >74% with NF-1. prevalence increases with age 90% of adults / 25% of children
 4. Two or more **neurofibromas** or one plexiform neurofibroma.
 - A. **Neurofibromas**: involve the skin, or along peripheral nerves and blood vessels and viscera. Appear characteristically during adolescence or pregnancy. small, rubbery lesions with a slight purplish discoloration of the overlying skin.
 - B. **Plexiform neurofibromas**: evident at birth and result from diffuse thickening of nerve trunks that are frequently located in the orbital or temporal region of the face. The skin overlying is hyperpigmented to a greater degree than a café-au-lait spot. *Plexiform neurofibromas produce overgrowth of an extremity and a deformity of the corresponding bone.*
 5. A distinctive osseous lesion such as **sphenoid dysplasia** (which may cause pulsating exophthalmos) or **cortical thinning of long bones with or without pseudoarthrosis**.
 6. **Optic gliomas** ≈15% of patients with NF-1. Most are asymptomatic with normal or near-normal vision, but ≈20% have visual disturbances or precocious sexual development secondary to tumor invasion of the hypothalamus.
 7. first-degree relative with NF-1
- Patients with NF-1 are at risk for hypertension, which may result from renal vascular stenosis or a pheochromocytoma.
- **segmental neurofibromatosis**: Somatic mosaicism, in which an abnormality in one copy of the NF1 gene is present in some cells but not others, indicates a postzygotic mutation.



NOTE:
Scoliosis is the most common orthopedic manifestation of NF-1, although it is not specific enough to be included as a diagnostic criterion.

- Conversion disorder occurs in presence of witnesses

NF1 skin examination:
Should be carried out yearly

Macrosomia associated hemorrhages:
Macrosomia is associated with traumatic or device-assisted delivery → leads to intraparenchymal or subdural hemorrhage. These hemorrhages are usually small and do not require intervention.

Seizures as complication of bacterial meningitis:
They are focal, instead of generalized

- Nocturnal headaches and morning vomiting are red flags for intracranial pathology

LP in Neonates
Neonates don't experience herniation after LP as their open fontanelles relieve ICP



Neurofibromatosis type 2 [6]

- Age of symptom onset: between 18–24 years [2]
- Bilateral vestibular schwannomas (acoustic neuromas)
 - Located in the internal acoustic meatus, affecting the vestibulocochlear nerve
 - Can cause tinnitus, hearing loss, or vertigo
- Early-onset cataracts, usually bilateral
- Multiple cerebral and spinal tumors (especially meningiomas and ependymomas) [7]
- Other features: seizures, skin nodules, and/or cafe au lait spots (not specific for NF type 2)



In NF Type 2, the mutation is in chromosome Twenty-2 and the clinical findings (schwannoma and cataracts) manifest on 2 sides.

- NF-2 accounts for 10% of all cases of NF
- ✓ incidence of 1/50,000 (NF2 gene mutation)
- ✓ diagnosed when one of the following two features :
 1. bilateral eighth nerve masses consistent with acoustic neuromas as demonstrated by CT scanning or MRI.
 2. A parent, sibling, or child with NF-2 and either unilateral eighth nerve masses or any two of the following:
 - ♦ neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacities=50%.
- ✓ Bilateral acoustic neuromas are the most distinctive feature of NF-2.
- ✓ Symptoms of hearing loss, facial weakness, headache, or unsteadiness may appear during childhood
- ✓ café-au-lait spots and skin neurofibromas are classic findings in NF-1, they are much less common in NF-2.

Diagnostics

- MRI of the brain and spine with contrast: to detect e.g., neurofibromas, meningiomas
- Ophthalmological exam: to detect optic glioma in NF type 1
- Auditory testing: to detect acoustic neuromas in NF type 2
- Genetic testing: mutations in NF1 gene or NF2 gene

Treatment

- Excision or resection of tumors (e.g., meningiomas)
- Surgery for kyphoscoliosis in NF type 1
- Drugs targeting the mTOR pathway (e.g., sirolimus) to reduce tumor growth

Prognosis

- Increased mortality due to malignant transformation of tumors
- Average life expectancy
 - NF type 1: ~ 60 years [9]
 - NF type 2: ~ 40 years [10][11]

Differential diagnosis

- Cafe au lait spots
 - McCune-Albright syndrome
 - Fanconi anemia
 - Tuberous sclerosis
 - Ataxia telangiectasia
 - Noonan syndrome
 - Bloom syndrome [8]
 - Etiology: mutations in the BLM gene → deficient helicase enzyme
 - Clinical features
 - Short stature
 - Skin rash (butterfly shaped on nose and cheeks, photosensitive), telangiectasia of hands and arms, cafe-au-lait spots
 - Increased risk of cancer (e.g., leukemia)
- Schwannoma
 - Schwannomatosis
 - Sporadic vestibular schwannoma

COMPLICATIONS :

2. learning disability
3. scoliosis
4. macrocephaly
5. headache
6. peripheral nerve malignancy
7. pheochromocytoma
8. re-novascular hypertension
9. epilepsy
10. Malignancy is the most common cause of death.

Neurofibromatosis types 1 & 2

Diagnosis	NF1 (von Recklinghausen disease)	NF2 (central neurofibromatosis)
Gene mutation	NF1 tumor suppressor gene; codes the protein neurofibromin	NF2 tumor suppressor gene; codes the protein merlin
Location of mutated gene	Chromosome 17	Chromosome 22
Main clinical features	• Café-au-lait spots • Multiple neurofibromas • Lisch nodules	• Bilateral acoustic neuromas

Second: Tuberous sclerosis:

- autosomal dominant disorder
- characterized by hamartomas in many organs, especially the brain, eye, skin, kidneys, and heart.
- incidence is 1 in 10,000 births
- 2/3 sporadic, Germline mosaicism is uncommon (explains normal parents with affected children).

CLINICAL MANIFESTATIONS

- extremely heterogeneous disease with a wide clinical spectrum varying from severe mental retardation and seizures → normal intelligence and no seizures.
- The classic clinical features are:
 1. facial angiofibromas (**adenoma sebaceum**)
 2. mental retardation
 3. Severe epilepsy.
- < 50% of patients exhibit all three features.
- major signs are:
 1. **ungual fibromas**
 2. **retinal hamartomas**
 3. **hypopigmented macules**
 4. **shagreen patches**: plaques of skin specially lumbar and gluteal regions, develop in late childhood or early adolescence.
 5. **Sebaceous adenomas** develop between 4 and 6yr of age; they appear as tiny red nodules over the nose and cheeks
 6. **Renal angiomyolipoma**: may undergo malignant transformation, most common cause of death in adults with tuberous sclerosis.
 7. **cardiac rhabdomyoma** 50%: largest in prenatal life & infancy, rarely symptomatic.
 8. **brain tubers**: The characteristic brain lesion is a cortical tuber.
 9. **brain subependymal nodules**
 10. **astrocytomas**
 11. **ash-leaf spots** 90%: hypomelanotic macules, called, are present in infancy and best detected with a Wood lamp under UV light.
- Tuberous sclerosis is one of the most common causes of infantile spasms = intractable epilepsy, mental retardation; autism, hyperactivity.
- directly by MRI and indirectly by CT, shows periventricular calcifications within the nodule, especially around the foramen of Monro.



Tuberous sclerosis



Adenoma sebaceum

Shagreen patch



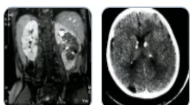
Ungual fibromas



HAMAARTOMASS: Hamartomas, **A**sh leaf spots, **M**ind (intellectual disability), **A**denoma sebaceum, renal **A**ngiomyolipoma, **R**habdomyoma, **T**umor suppressor genes (**T**SC1 gene and **T**SC2 gene), autosomal d**O**minant, **M**itral regurgitation, **A**strocytomas, **S**eizures, and **S**hagreen patches.

Diagnostics [16]

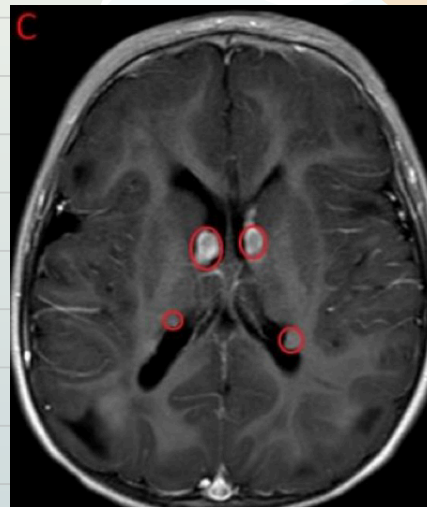
- **ECG**: cardiac rhabdomyoma can cause ventricular hypertrophy and arrhythmias
- **EEG**: seizure activity
- **Imaging**
 - Echocardiography: rhabdomyoma (common in the apex of the left ventricle)
 - Abdominal MRI: renal cyst, angiomyolipoma, and/or carcinoma
 - Contrast cerebral CT/MRI
 - Tumors (e.g., giant cell astrocytomas)
 - Enlarged ventricles (tumors in the periventricular area commonly cause obstructive hydrocephalus)
- **Genetic testing**: mutation of TSC1 or TSC2 gene



Treatment [16]

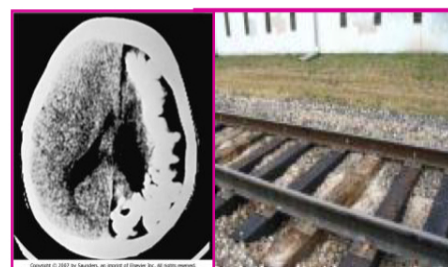
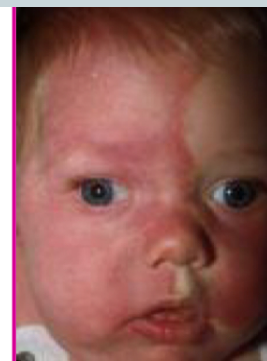
- **Seizure control**
 - Infantile spasms: vigabatrin or ACTH
 - Anticonvulsants
- **mTOR inhibitors**: to treat renal angiomyolipoma and inoperable giant cell astrocytoma
- **Removal of angiofibroma** (laser treatment or electrosurgery)
- **Surgery** in the case of:
 - Obstructive hydrocephalus (with ↑ ICP)
 - Drug-resistant seizures

Tuberous sclerosis complex	
Pathophysiology	• Mutation (inherited or de novo) in TSC1 or TSC2 gene • Autosomal dominant
Clinical features	• Dermatologic ◦ Ash-leaf spots ◦ Angiofibromas of the malar region ◦ Shagreen patches • Neurologic ◦ CNS lesions (eg, subependymal tumors) ◦ Epilepsy (eg, infantile spasms) ◦ Intellectual disability ◦ Autism & behavioral disorders (eg, hyperactivity) • Cardiovascular: rhabdomyomas • Renal: angiomyolipomas
Surveillance	• Tumor screening ◦ Regular skin & eye examinations ◦ Serial MRI of the brain & kidney ◦ Baseline echocardiography & serial ECG • Baseline electroencephalography • Neuropsychiatric screening



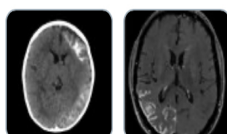
Third: Sturge-Weber syndrome:

- Sturge-Weber syndrome is sporadic and not genetic.
- characterized by **angiomas of the leptomeninges** overlying the cerebral cortex in + **ipsilateral facial port-wine nevus** that at the least, covers part of the forehead and upper eyelid.
- **The nevus** may more extensive and with bilateral distribution. (ectasia of superficial venules, not a hemangioma, because it has no endothelial proliferation).
- **Ocular defects** of Sturge-Weber syndrome include:
 1. glaucoma: 30% to 50%, progressive.
 2. hemangiomas of the choroid, conjunctiva, and episclera.
- **seizures** The most common associated neurologic abnormality. Due to brain ischemic injury by the meningeal angiomas.
 - ✓ most patients in the 1st year of life
 - ✓ They are focal tonic-clonic and contralateral to the side of the facial nevus.
- **mental retardation** is common, at least 50% in later childhood.
- **Angiomas**, most commonly located in the posterior parietal, posterior temporal, and anterior occipital lobes, within the pia mater.
 - ✓ hemiparesis, hemianopia, intractable focal seizures, and dementia.
- **"tram track" or "railroad track" calcifications** is seen in about 60% of cases.



Diagnostics

- **Eye exam:** IOP measurement to rule out glaucoma
- **EEG:** to detect seizure activity
- **Imaging**
 - **CT or skull radiograph:** gyriform, curvilinear, parallel opacities with a **tram-track appearance**
 - **MRI of the brain with contrast:** enhancement of leptomeningeal angiomas
 - **Angiography:** to detect abnormal vessel structure
- **Genetic testing:** mutation in GNAQ gene
- **CSF analysis:** elevated protein in case of secondary microhemorrhage



Treatment

- Seizure control: anticonvulsants or surgery
- Glaucoma management: See "Treatment" in glaucoma.
- Pulsed laser therapy for removal of port-wine stain
- Low-dose aspirin to prevent stroke-like episodes [27]

To Sum up:

1. Facial port wine stain
2. Leptomeningeal capillary-venous malformation
3. Intellectual disability
4. Seizures
 - a. Originate focally and then become generalized
5. Glaucoma
6. Visual field defects (eg, homonymous hemianopia)
7. Diagnosis
 - a. MRI of brain with contrast
 - i. Detects intracranial vascular malformations

Sturge-Weber syndrome	
Pathophysiology	Mutation in <i>GNAQ</i> gene
Clinical features	- Port wine stain (trigeminal nerve [CN V1/V2] distribution) - Leptomeningeal capillary-venous malformation - Seizures $\pm$ hemiparesis - Intellectual disability - Visual field defects - Glaucoma
Diagnosis	MRI of the brain with contrast
Management	- Laser therapy - Antiepileptic drugs - Intraocular pressure reduction

Overview of neurocutaneous syndromes

Disorder	Cause		Main features		
	Inheritance	Mutation	Skin changes	Common tumors	Other features
Neurofibromatosis type 1	Autosomal dominant	NF1 gene on chromosome 17	- Cafe au lait spots - Axillary/inguinal freckling	- Multiple neurofibromas - Optic glioma - Pheochromocytoma	Lisch nodules
Neurofibromatosis type 2	Autosomal dominant	NF2 gene on chromosome 22	Cafe au lait spots (nonspecific)	- Bilateral vestibular schwannoma - Meningioma - Ependymoma	Bilateral cataracts
Tuberous sclerosis	Autosomal dominant	- TSC1 gene on chromosome 9 - TSC2 gene on chromosome 16	- Ash leaf spots - Shagreen patch - Adenoma sebaceum - Ungual fibromas	- Giant cell astrocytoma - Cardiac rhabdomyoma - Renal angiomyolipoma	- Infantile spasms - Intellectual disability
Sturge-Weber syndrome	Not inherited	Somatic mutation in <i>GNAQ</i> gene	Port-wine stain	Leptomeningeal angioma	- Seizures - Intellectual disability - Stroke-like episodes

Weakness and Hypotonia

First: Guillain-Barré syndrome:

Summary

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyneuropathy that typically manifests with bilateral ascending flaccid paralysis and sensory involvement, e.g., paresthesia. The pathogenesis of GBS involves autoantibodies against antigens in the myelin sheath, other Schwann-cell antigens, and axon membranes. Approximately 65% of patients have an upper respiratory tract or gastrointestinal infection before the onset of GBS symptoms. Diagnosis is primarily clinical; alternative diagnoses should be considered especially in patients with atypical presentations. Cerebrospinal fluid (CSF) analysis showing albuminocytologic dissociation and electrodiagnostic study findings help support the diagnosis. Medical treatment depends on the severity of symptoms; available treatment options are intravenous immunoglobulin (IVIg) and plasmapheresis. Close monitoring is required for all patients. Complications such as respiratory failure, pulmonary embolism, and/or cardiac arrest increase mortality. Up to 20% of patients remain severely disabled and approximately 5% of patients die despite medical treatment.

- postinfectious autoimmune peripheral neuropathy that often occurs after a respiratory or gastrointestinal infection.
- Infection with *Campylobacter jejuni* is associated with a severe form of the illness.

Pathophysiology

- Postinfectious autoimmune reaction that generates cross-reactive antibodies (**molecular mimicry**) [7]
- Infection triggers humoral response → formation of autoantibodies against gangliosides (e.g., GM1, GD1a) or other unknown antigens of peripheral Schwann cells → immune-mediated **segmental demyelination** → **axonal degeneration** of motor and sensory fibers in peripheral and cranial nerves (CN III–XII) [7]

CLINICAL MANIFESTATIONS:

- The characteristic symptoms are :
 5. areflexia
 6. flaccidity
 7. symmetric weakness beginning in legs and ascending to the arms, trunk, throat, & face.
- Progression can occur rapidly, in hours or days, or more indolently, over weeks.
- Typically the child complains of numbness or paresthesia in the hands and feet, then experiences a "heavy," weak feeling in the legs → inability to climb stairs or walk.
- Objective signs of sensory loss are minor compared with the dramatic weakness
- Progression to bulbar and respiratory insufficiency may occur rapidly.
- **Dysfunction of autonomic:**
 1. hypertension, hypotension, orthostatic hypotension
 2. tachycardia & other arrhythmias
 3. urinary retention or incontinence
 4. stool retention
 5. episodes of abnormal sweating
 6. flushing
 7. peripheral vasoconstriction.
- This polyneuropathy can be difficult to distinguish from an acute spinal cord syndrome.
- Preservation of bowel and bladder function, loss of arm reflexes, absence of a sensory level, and lack of spinal tenderness → Guillain-Barré syndrome.
- **Miller Fisher variant** : cranial nerve variant of Guillain-Barré syndrome manifests with ataxia, partial ophthalmoplegia, and areflexia.

- D/D:
 1. Porphyria
 2. tick paralysis
 3. vasculitis
 4. nutritional deficiency (vitamins B₁, B₁₂, and E)
 5. endocrine disorders
 6. infections (diphtheria, Lyme disease)
 7. toxins (organo-phosphate, lead).
- may resolve spontaneously
- 75% of patients recover normal function within 1 to 12 months.
- 20% of patients are left with mild to moderate residual weakness in the feet and lower legs.
- The mortality rate is 5%, and death is caused by:
 3. autonomic dysfunction (hyper-hypotension, tachy-bradycardia, and sudden death)
 4. respiratory failure
 5. complications of mechanical ventilation
 6. cardiovascular collapse
 7. pulmonary embolism.

LABORATORY AND DIAGNOSTIC STUDIES

- The CSF in Guillain-Barré syndrome is often normal in the first days of the illness → elevated protein levels without significant pleocytosis.
- NCV and EMG also may be normal early in the disease → delay in motor NCV and decreased amplitude and temporal dispersion of the evoked compound motor action potential

TREATMENT

- Moderate or severe weakness or rapidly progressive weakness → **pediatric ICU**.
- **Endotracheal intubation** in patients who exhibit early signs of hypoventilation, accumulation of bronchial secretions, or obtunded pharyngeal or laryngeal reflexes.
- **Plasma exchange and IV immunoglobulin** are beneficial in rapidly progressive disease.
- Most patients are treated initially with **IV immunoglobulin** (total dose 1 to 2 g/kg/day given for 4 to 5 days).

Guillain-Barré syndrome	
Etiology	• Upper respiratory tract or gastrointestinal infections, e.g. C. jejuni enteritis, CMV, HIV, Zika virus
Symptom onset	• 1-6 weeks following an upper respiratory tract or gastrointestinal tract infection
Motor findings	• Ascending paralysis • Involvement of respiratory muscles
Reflexes	• Reduced or absent
Sensory findings	• Peripheral, symmetrical paresthesias with a stocking-glove distribution • Neuropathic pain
Autonomic dysfunction	• Arrhythmia • Hypertension or hypotension • Urinary retention • Intestinal dysfunction
Cranial nerve involvement	• Bilateral facial nerve involvement (facial diplegia)
CSF examination	• Albuminocytologic dissociation (elevated protein levels, normal WBC count)
Imaging and findings	• Usually normal • Nerve root enhancement on MRI (with contrast) may support the diagnosis of GBS.^[9]
Electrophysiological findings	• Decreased nerve conduction velocity

To sum up:

1. Demyelination of peripheral nerves

- Ascending paralysis
 - Symmetric weakness
- Weak or absent deep tendon reflexes
- Respiratory failure
- Autonomic symptoms
 - BP/HR instability (arrhythmias)
 - Ileus

2. Preceding respiratory or GIT infection

3. Management

- If Guillain-Barre is suspected in a stable patient, the very next step is to assess pulmonary function with **spirometry**
 - FVC** and **negative inspiratory force** monitor respiratory muscle strength
 - A decline in FVC (≤ 20 mL/kg) indicates impending respiratory failure → do endotracheal intubation
 - Additional indications for elective intubation are: **respiratory distress**, severe **dysautonomia** (eg, HR and BP instability) or **widened pulse pressure**
- Treatment
 - IV immunoglobulin
 - Plasmapheresis

Guillain-Barré syndrome	
Pathophysiology	• Immune-mediated demyelinating polyneuropathy • Preceding gastrointestinal (<i>Campylobacter</i>) or respiratory infection
Clinical features	• Paresthesia, neuropathic pain • Symmetric, ascending weakness • Decreased/absent deep-tendon reflexes • Autonomic dysfunction (eg, arrhythmia, ileus) • Respiratory compromise
Diagnosis	• Clinical • Supportive findings ◦ Cerebrospinal fluid: ↑ protein, normal leukocytes ◦ Abnormal electromyography & nerve conduction
Management	• Monitor autonomic & respiratory function • Intravenous immunoglobulin or plasmapheresis



Second: Hereditary motor sensory neuropathy : (Charcot-Marie-Tooth Syndromem)

- chronic, genetic polyneuropathy characterized by weakness and wasting of distal limb muscles.
- The most common form (Charcot-Marie-Tooth type 1A)
- HMSN type II : neuronal form with mildly decreased NCV and no hypertrophic changes.
- Type I HMSN and type II HMSN are inherited as autosomal dominant traits with variable expressivity.

CLINICAL MANIFESTATIONS:

- complaints begin in the preschool years with **pes cavus deformity of feet** and weakness of the ankles with frequent tripping
- Early Examination:
 1. high-arched feet
 2. bilateral weakness of foot dorsiflexors
 3. Normal sensation despite occasional complaints of paresthesia.
- Progression of HMSN is slow, extending over years and decades
- patients develop weakness and atrophy of the entire lower legs and hands and mild to moderate sensory loss in the hands and feet.
- Some patients never have more than a mild deformity of the feet & loss of ankle reflexes.

LAB STUDIES:

- HMSN type I is a demyelinating illness with severely decreased NCV and hypertrophic changes on nerve biopsy.

TREATMENT

- No specific treatment.

- Progressive disease of peripheral nerves; **peroneal muscle atrophy; peroneal and tibial nerves**
- Autosomal dominant
- Clinical presentation
 - Asymptomatic until late childhood or adolescence but may have problem with gait as early as age 2 years
 - **Clumsy, fall easily; muscles of anterior compartment of lower leg become wasted → stork-like appearance**
 - **Pes cavus, foot drop**
 - **Claw hand** (in worse cases)
 - **Slowly progressive** through life, but normal lifespan and remain ambulatory
- Diagnosis
 - CPK is normal.
 - **Decreased nerve conduction velocities** (motor and sensory)
 - **Sural nerve biopsy** is diagnostic.
 - Blood molecular genetic diagnosis
- Treatment
 - **Stabilize ankles**
 - **Surgical ankle fusion**
 - **Protection from trauma**
 - **If sensory problems, phenytoin or carbamazepine**

Muscular dystrophy

First: Duchenne dystrophy:

- sex-linked recessive Muscular dystrophy
- 1/3 cases represent new mutations.
- Appearing in 20 to 30 per 100,000 boys.
- The disease results from absence of a large protein called **dystrophin** that is associated with the muscle fiber plasma membrane.
- **Becker muscular dystrophy:**
 - ✓ rises from an abnormality in the same gene locus that results in the presence of dystrophin that is abnormal in either amount or molecular structure.
 - ✓ It has the same clinical symptoms as Duchenne dystrophy
 - ✓ Later onset and slower progression.

CLINICAL MANIFESTATIONS:

- At 2 to 3 years of age, boys develop an awkward gait and an inability to run properly.
- Some have an antecedent history of mild slowness in attaining motor milestones, such as walking and climbing stairs.
- Examination:
 1. firm calf hypertrophy
 2. mild to moderate proximal leg weakness exhibited by a hyperlordotic
 3. waddling gait
 4. Inability to arise from the ground easily.
 5. **Gower sign:** child typically arises from a lying position on the floor by using his arms to "climb up" his legs and body.
- Arm weakness is evident by 6 years of age.
- Most boys are confined to a wheelchair by 12 years of age.
- By age 16, little mobility of arms remains, and respiratory difficulties increase.
- Death is caused by pneumonia or congestive heart failure from myocardial involvement.

- Progressive muscle **paresis** and **atrophy**
 - Starts in the proximal lower limbs (pelvic girdle)
 - Extends to the upper body and distal limbs as the disease progresses
- **Weak reflexes**
- Waddling gait (i.e., Duchenne limp) with bilateral Trendelenburg sign
- **Gower maneuver**
 - The individual arrives at a standing position by supporting themselves on their thighs and then using the hands to "walk up" the body until they are upright.
 - Classic sign of DMD, but also occurs in inflammatory myopathies (e.g., dermatomyositis, polymyositis) and other muscular dystrophies (e.g., BMD)
- **Calf pseudohypertrophy** (see pathophysiology above)
- **Scoliosis**
- Inability to walk by approx. 12 years of age
- Cardiac and respiratory muscle involvement
 - **Dilated cardiomyopathy:** common cause of death
 - Cardiac arrhythmias
 - Respiratory insufficiency
- Cognitive impairment
- In late stages: nocturnal hypoventilation, dysphagia, vomit, diarrhea, and constipation; rarely intestinal pseudo-obstruction

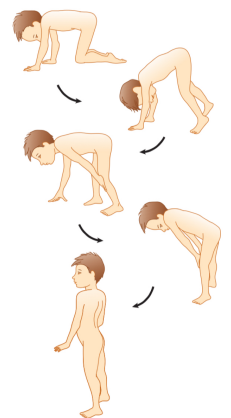


Figure 21-3. Gower Sign in Duchenne Muscular Dystrophy

DIAGNOSTIC STUDIES:

- Serum creatine phosphokinase levels are always markedly elevated.
- Muscle biopsy specimen shows muscle fiber degeneration and regeneration accompanied by increased intrafascicular connective tissue.
- Diagnosis is by DNA probe for Duchenne muscular dystrophy.
- Prenatal diagnosis of both diseases is possible by genetic testing.

TREATMENT

- Supportive care includes physical therapy, bracing, proper wheelchairs, and prevention of scoliosis.

Second: Myotonic dystrophy:

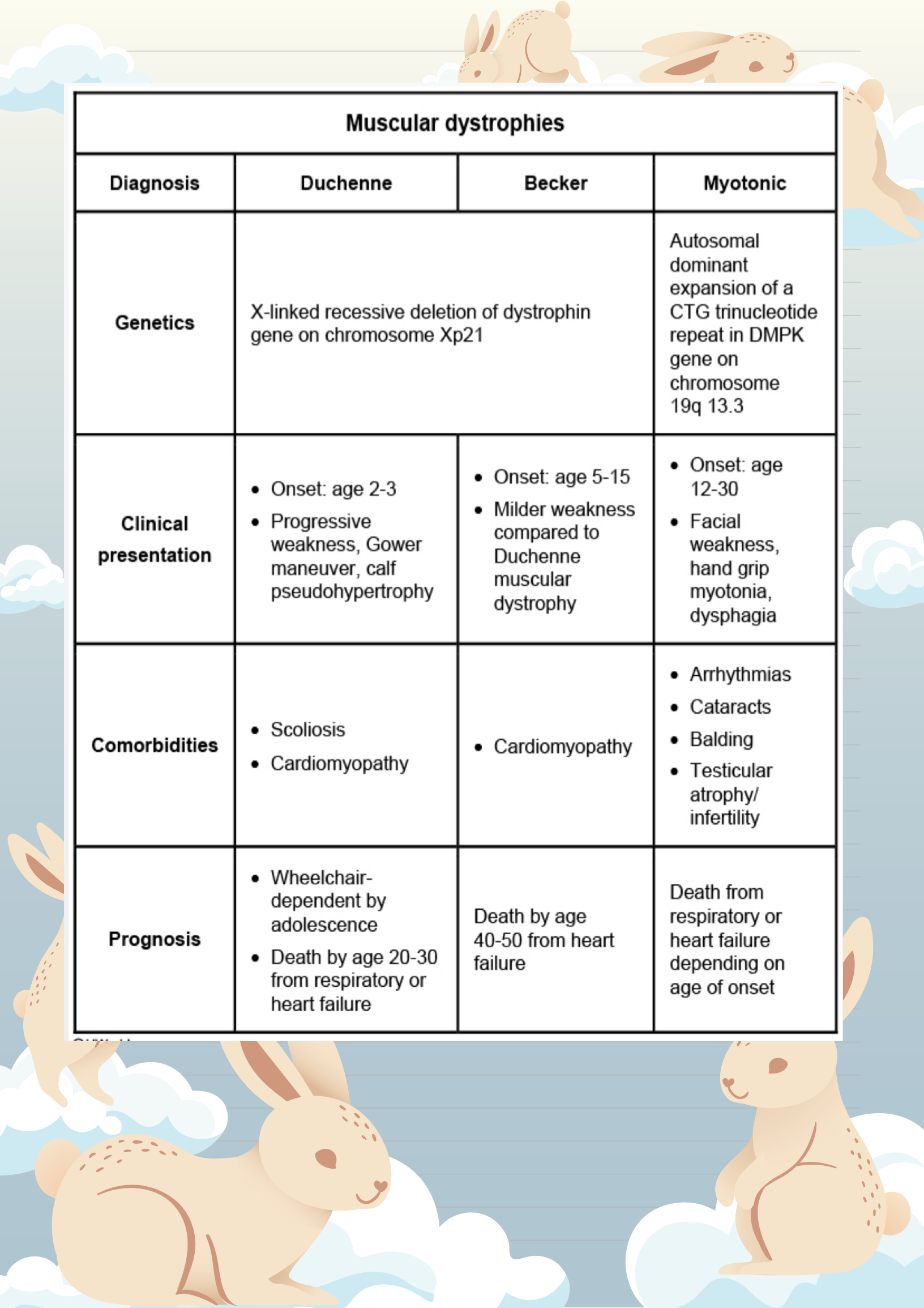
- autosomal dominant genetic disease
- Myotonia is a disorder of muscle relaxation
- caused by progressive expansion of a triplet repeat, GCT, on chromosome 19 in a gene designated myotonin protein kinase (*MP-PK*).
 1. birth, with severe generalized hypotonia and weakness
 2. adolescence, with slowly progressive facial and distal extremity weakness and myotonia.
- The adolescent type is the classic illness and is associated with:
 1. cardiac arrhythmias
 2. cataracts
 3. male pattern baldness
 4. infertility in males (hypogonadism).
- The facial appearance is characteristic "hatchet face "
 1. hollowing of muscles around temples, jaw, and neck
 2. ptosis
 3. facial weakness
 4. drooping of the lower lip.
- The voice is nasal and mildly dysarthric.
- Some myotonic dystrophy mothers give birth to infants with the disease who :
 1. mobile and hypotonic
 2. expressionless faces
 3. tented upper lips
 4. ptosis
 5. absence of sucking and Moro reflexes
 6. poor swallowing and respiration
 7. weakness and atony of uterine smooth muscle during labor lead to associated hypoxic-ischemic encephalopathy and its sequelae.
 8. presence of clubfoot or a history of poor fetal movements indicates intrauterine neuromuscular disease.



To sum up:

1. Autosomal dominant
2. Physical examination
 - a. Ptosis
 - b. Temporal wasting
 - c. Thin cheeks
 - d. Emaciated extremities
 - e. Atrophy of thenar and hypothenar eminences
 - f. Inverted V-shaped upper lip
 - g. Testicular atrophy
 - h. Delayed relaxation
3. All muscles are affected:
 - a. Skeletal muscles
 - i. Prominent in face, forearms, hands and ankle dorsiflexors (eg, bilateral foot drop)
 - b. Smooth muscles
 - i. Dysphagia → ↑risk of aspiration pneumonia
 - c. Cardiac muscle
 - i. Conduction problems → arrhythmia
4. Other manifestations are:
 - a. Cataract
 - b. Testicular atrophy/infertility
 - c. Frontal baldness
 - d. Insulin resistance

Myotonic dystrophy	
Genetics	• Autosomal dominant • CTG trinucleotide repeat expansion • Repeat length inversely correlating with age of onset
Clinical presentation	• Myotonia (delayed muscle relaxation) • Progressive muscle weakness (eg, face, hands) • Childhood form: cognitive & behavioral problems • Infantile form: hypotonia, arthrogryposis
Associated findings	• Arrhythmias • Cataracts • Excessive daytime sleepiness • Testicular atrophy/infertility
Diagnosis	• Genetic testing
Treatment	• Symptomatic care



Muscular dystrophies			
Diagnosis	Duchenne	Becker	Myotonic
Genetics	X-linked recessive deletion of dystrophin gene on chromosome Xp21		Autosomal dominant expansion of a CTG trinucleotide repeat in DMPK gene on chromosome 19q 13.3
Clinical presentation	- Onset: age 2-3 - Progressive weakness, Gower maneuver, calf pseudohypertrophy	- Onset: age 5-15 - Milder weakness compared to Duchenne muscular dystrophy	- Onset: age 12-30 - Facial weakness, hand grip myotonia, dysphagia
Comorbidities	- Scoliosis - Cardiomyopathy	Cardiomyopathy	- Arrhythmias - Cataracts - Balding - Testicular atrophy/infertility
Prognosis	- Wheelchair-dependent by adolescence - Death by age 20-30 from respiratory or heart failure	Death by age 40-50 from heart failure	Death from respiratory or heart failure depending on age of onset