NEUROLOGY BOOK SUMMARY

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CHAPTER 9: HEADACHE AND FACIAL PAIN

- **Headaches** → 1- Primary headache syndrome (uncertain pathogenesis). 2- Secondary headaches (defined pathophysiological basis).
- **Secondary Headaches**: 1- Disorders of intracranial pressure. 2- Idiopathic intracranial Hypertension. 3- Meningeal irritation. 4- Giant cell arteritis (cranial/temporal arteritis). 5- Other causes.
- **Disorders of intracranial pressure**:
    - Headache of raised intracranial pressure (cranial tumor): Present on waking or may wake the patient at night, it may improve later in the day.
    - Exacerbated by Sneezing, Straining, Bending, Lifting, Lying down.
    - Short duration history with crescendo quality to symptoms (the pain becoming increasingly severe and persistent).
    - Associated with nausea and vomiting.
    - **Effortless vomiting, with or without associated nausea** → mass in the posterior fossa, close to the fourth ventricle, irritating the vomiting center.
    - Headache of low intracranial pressure: related to posture, pain rapidly relieved by lying down.
    - Most commonly associated with Lumbar puncture.
- **Idiopathic Intracranial Hypertension: (Pseudotumor cerebri)**
    - It occurs in young, obese women, with signs and symptoms of raised intracranial pressure but no mass lesion on CT or MR.
    - **Pathophysiology**: incompletely understood, may involve impaired CSF absorption.
    - **Present with**: 1- Morning headache. 2- Vomiting. 3- Diplopia. 4- Visual obscuration (sudden, transient bilateral visual loss with changes in posture). 5- Tinnitus. 6- Bilateral papilledema. 7- Unilateral or bilateral 6^{th} nerve palsies (false localizing sign).
    - Do CT to exclude mass lesions and reveal ventricles of normal size.
    - CSF examination by lumbar puncture (safe after excluding mass lesion) reveals 1- raised pressure (>40 cm of CSF) 2- normal CSF contents.

    - **Treatment**: 1- Self-limiting (resolve completely with weight loss and few lumbar punctures). 2- chronic cases with a threat to vision from secondary optic atrophy (medical treatment with 1- **carbonic anhydrase inhibitor; acetazolamide**. 2- **diuretics**; **chlortalidone**. 3- **corticosteroids**). 3- Surgical intervention (Lumboperitoneal shunt to drain CSF / Fenestration procedure to protect the optic nerve).
- **Meningeal irritation**:
    - Irritation of the meninges by inflammatory process or blood, producing severe global or occipital headache with vomiting and exacerbation of symptoms by bright light (photophobia) and neck stiffness (nuchal rigidity – resistance to passive neck flexion-).
    - **Subarachnoid hemorrhage**: very sudden onset severe pain, and the patient may lose consciousness.
    - **Kernig's sign**: pain and resistance to passive knee extension with the hip flexed.
    - In children, nuchal rigidity → Posterior fossa mass rather than meningeal process (negative Kernig's).
- **Giant cell arteritis**:
    - Elderly >50, Granulomatous changes in branches of the external carotid (superficial temporal) and intracranial vessels and blood supply to the optic nerve head.
    - **Etiology**: uncertain, but viral infection and autoimmunity have been implicated.
    - **Presentation**: 1- Headache (non-specific, localize to the temples + tenderness). 2- Scalp tenderness (when combing). 3- Pain on chewing (low blood supply to muscles of mastication – intermittent claudication of the jaw-). 4- Skin ulceration rarely. 5- Amaurosis fugax (transient loss of vision in one eye, patient at risk of permanent monocular or complete blindness). 6- Diplopia (3^{rd} or 6^{th} nerve involvement). 7- Constitutional symptoms (low grade fever, night sweats, shoulder or pelvic girdle pain, malaise, anorexia, weight loss). 8- evidence of more generalized arteritis (disturbance of liver function, peripheral neuropathy, involvement of intracranial vessels; stroke).

    - **Investigations**: 1- ESR & CRP (elevated). 2- Other blood tests (normochromic normocytic anemia, abnormal LFT; raised ALP). 3- Temporal artery biopsy.
    - Negative biopsy doesn't exclude diagnosis due to skip lesions.
    - **Treatment**: 1- IV hydrocortisone after blood sampling (excellent response).
    - If patients improved after 24-48h, taper the dose according to symptoms and ESR, but continue treatment for 18 months – 2 years.
    - **Polymyalgia Rheumatica**: Girdle pains and morning stiffness with some constitutional upsets without cranial manifestations, responds to corticosteroids but to lower doses than GCA.
- **Other causes**:
    - **Stroke**: especially when caused by Hemorrhage, Intracranial venous thrombosis, Arterial dissection.
    - **Metabolic disturbances**: like hypoxia, hypercapnia, and hypoglycemia.
    - **Vasoactive drugs and other substances**.
- **Primary Headache Syndromes**: 1- Migraine. 2- Cluster headache. 3- Tension-type headache. 4- Chronic daily headache.
- **Migraine**:
    - Periodic disorder, characterized by unilateral (or bilateral) headache which may be associated with vomiting and visual disturbances.
    - Common, may develop at any age (typically teens or twenties), women are more commonly affected, positive family history, related to HTN and head injury.
    - **Pathophysiology**: Initial neurological symptoms (aura) attributed to a phase of intracerebral vasoconstriction, subsequent vasodilation of extracerebral vessels of the scalp lead to headache. Serotonin pathways and Calcium channels also play a role.
    - **Triggers**: 1- Stress (after it's over). 2- Physical exercise. 3- Diet (alcohol, cheese, chocolate, red wine). 4- Hormones (following the menarche).

- **Clinical features**:
  - **Migraine with aura (classical migraine)**: 1- Vague prodromal symptoms preceding the attack (drowsiness, mood changes, hunger, anorexia). 2- Aura (lasts 15-20 mins, maybe 1h). 3- Scotomata (may scintillate – teichopsia-). 4- Crenated or castellated patterns (fortification spectra). 5- homonymous hemianopia or complete blindness. 6- unilateral numbness or paresthesia of face, arm and leg. 7- dysphasia and limb weakness (rare). 8- headache (unilateral, periorbital, contralateral to the side of hemianopia).
    - Pain exacerbated by coughing, straining, or bending (Jolt phenomena)
    - Patients prefer to lye in a dark room.
    - **Associated symptoms**: 1- Photophobia. 2- Nausea. 3- Vomiting. 4- Pallor. 5- Diuresis.
  - **Migraine without aura (common migraine)**: No aura, but some vague prodromal symptoms, headache on waking, otherwise similar to classical migraine.
  - **Basilar migraine (Bickerstaff variant)**: affects teenage female patients, prominent features suggestive of vertebrobasilar ischemia during the aura (vertigo, diplopia, dysarthria, ataxia, syncope).
  - **Hemiplegic and Ophthalmoplegic migraine**: rare syndromes in which headache is accompanied by hemiplegia or ophthalmoplegia with focal neurological signs, should be diagnosed after structural causes like aneurysm have been excluded.
- **Diagnosis**: 1- almost exclusively on History (episodes of headache lasting <3 days followed by pain free periods from days to months). 2- Neurological exam is normal (except during an attack of hemiplegic or ophthalmoplegic or cerebral infection). 3- Cranial bruit (migraine associated with vascular malformation).
- **Status migrainosus**: continuous headache week after week.

- **DDx**: 1- Migraine (slower than the others). 2- Transient cerebral ischemia. 3- Epilepsy.
- **Management**:
  - **Acute attacks**: 1- Lying in a darkened room and sleep. 2- Simple analgesics (paracetamol or aspirin) + antiemetics. 3- if not responding → Ergotamine (vasoconstrictor) / Triptans; Sumatriptan (Serotonin receptor agonist)
    - **Ergot alkaloids may cause acute poisoning (ergotism)**: 1- vomiting. 2- muscle pain. 3- weakness. 4- paresthesia in the extremities. 5- chest pain. 6- pruritis. 7- cardiac dysrhythmia. 8- gangrene with chronic use (contraindicated in peripheral vascular disease).
    - **Sumatriptan interacts with** 1- Ergotamine. 2- Monoamine oxidase inhibitors. 3- Selective Serotonin reuptake inhibitors. 4- Lithium.
    - The use of sumatriptan and ergotamine is contraindicated in patients with IHD.
  - **Prophylaxis**: 1- avoid clear-cut dietary products. 2- use estrogen containing preparations (oral contraceptives and hormonal replacement therapy) with caution. 3- first line agents include Propranolol (beta blocker) and Pizotifen (serotonin receptor antagonist) → for 3-6 months to reduce the frequency of the attacks without recurrence on withdrawals. 4- sodium valproate. 5- verapamil. 6- topiramate. 7- methysergide (serotonin receptor antagonist , restricted use to patients with severe and frequent migraines unresponsive to other agents). 8- Tricyclic antidepressants; amitriptyline (in patients who have coexistent tension-type headache).
    - **Beta blockers are contraindicated in** 1- uncontrolled heart failure. 2- obstructive airway disease. 3- severe peripheral vascular disease. 4- cardiac bradyarrhythmia.

        - **Side effects**: 1- Pizotifen causes drowsiness and weight gain + anticholinergic effect (limited use in patients with glaucoma and urinary retention). 2- Methysergide causes retroperitoneal fibrosis

- **Cluster headache**:
    - Male, 20-60 years old, severe attacks of pain around one eye (always the same side), lasts 20-120 mins, may recur several times a day, waking the patient several times at night.
    - Alcohol precipitates the attack.
    - It continues for days, weeks or months, then the patient become symptom free for many months or even years.
    - Unlike migraine, patients are often restless during the attacks and appear pale.
    - Pain associated with conjunctival injection, lacrimation, nasal discharge and congestion, Horner's syndrome may develop and persist after the attack.
    - **Treatment**: 1- high flow 100% oxygen. 2- ergotamine. 3- sumatriptan. 4- corticosteroids. 5- longer treatment to prevent recurrence with methysergide, verapamil, pizotifen. 6- Lithium is helpful for chronic clusters (but continuously monitor blood levels).
    - **Other DDx**: trigeminal autonomic syndromes → respond well to indomethacin.
- **Tension-type headache**:
    - Very common, unknown cause, though abnormal contraction of muscles of the head and neck, triggered by psychogenic factors (anxiety and depression) or by local disease of the head and neck (cervical spondylosis).
    - Varies from dull pain at various sites to global pressure sensation to the feeling of a tight band around the head, no associated symptoms and neurological examination is normal, migraine and tension-type headache often coexist.
    - **Treatment**: 1- reassurance that there is no sinister underlying cause. 2- tricyclic antidepressants; amitriptyline for 3-6 months. 3-

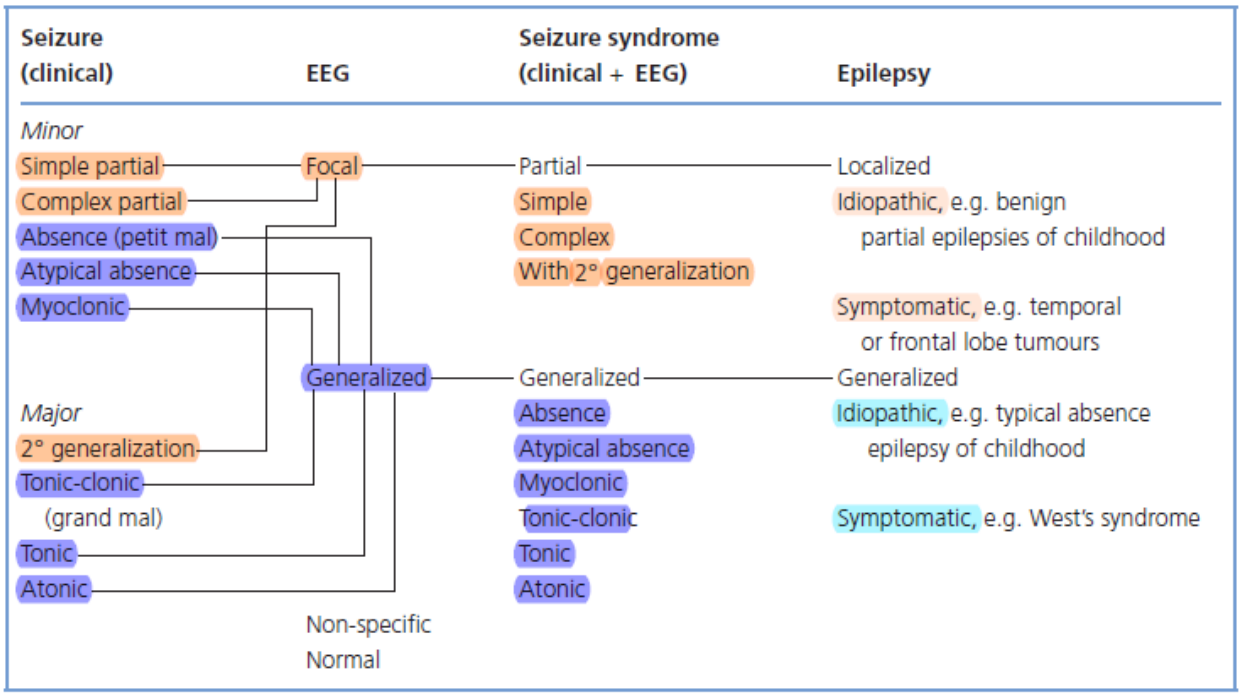
relate to a psychotherapist (relaxation exercises, psychotherapy; stress management).

- **Chronic daily headache**:
  - Headache occurring 15 or more days per month, caused by secondary headache syndromes, chronic tension-type headache, transformed migraine, medication overuse (analgesics, triptans, ergotamine) which convert an episodic headache syndrome into a chronic condition.
  - **Withdrawal of the overused medications**: transitional strategies to cover the period of withdrawal with NSAIDs/steroids, antiemetics, dihydroergotamine.
  - **Preventive measures**: Tricyclic antidepressants.
- **Facial pain**:
  - **Trigeminal neuralgia**:
    - Patients over 50, due to compression of the trigeminal sensory root adjacent to the brainstem.
    - Idiopathic or Symptomatic (tumors of cerebellopontine angle, multiple sclerosis).
    - Present with unilateral lancinating (brief, severe, sharp, stabbing, electrical) facial pain in the distribution of one or more divisions of the trigeminal nerve (most commonly mandibular and maxillary branches).
    - There are trigger areas, where a gentle pressure causes pain (can't wash their faces, can't shave, even talk or cold breeze can cause pain), weight loss due to food avoidance.
    - **Glossopharyngeal neuralgia**: similar syndrome (rarer), pain in the throat or deep inside the ear.
    - May have Tic Douloureux (involuntary facial spasms due to anxiety about trigger areas)
    - **Diagnosis**: MR
    - **Treatment**: 1- Carbamazepine. 2- if carbamazepine failed → Baclofen, Phenytoin, Sodium valproate, Gabapentin, Clonazepam, Tricyclic antidepressants. 3- if still no response→ Surgery.
  - **Post-herpetic neuralgia**:

        - In patients who suffered Shingles in one of the branches of the trigeminal nerve (Zoster ophthalmicus), persistent facial pain after the rash has healed, very severe and intractable lasting 2-3 years.
        - Responds to Tricyclic antidepressants, Carbamazepine, Topical application of Capsaicin.
    - **Atypical facial pain**:
        - Constant facial pain in non-anatomical distribution and with no local cause.
        - Benefit from Tricyclics.

CHAPTER 10: EPILEPSY

- **Epilepsy**: occasional, sudden, excessive, rapid and local discharges of gray matter.
- **Clinically**: paroxysmal disorder in which cerebral cortical neuronal discharges result in intermittent stereotyped attacks of altered consciousness, motor or sensory function, behavior or emotion.
- **Classification according to the onset**: 1- Focal (partial) seizures. 2- Generalized Seizures.
- **Partial seizure**: 1- Simple partial (consciousness is retained throughout the attack). 2- Complex partial (consciousness is impaired at any stage).
- Partial seizures may become Secondarily generalized (the patient losing consciousness with clinical evidence of spread across the cortex; bilateral convulsive movements).
- **Another classification**: 1- Idiopathic (most patients; strong inherited predisposition). 2- Symptomatic



- Up to 1% of the general population suffer from active epilepsy.
- **Status Epilepticus**: uncontrolled series of seizures, the patient failing to regain consciousness between attacks.
- **Primary Generalized Epilepsy (Tonic-Clonic / Grand mal)**:

    - Often begins in childhood, the most common type of seizure in adults.
    - **Present with**: 1- vague symptoms of dizziness or irritability preceding the attack. 2- Epileptic cry. 3- the patient loses consciousness and falls to the ground.
    - **The initial Tonic phase** → Generalized muscle spasms, lasting only few seconds.
    - **The subsequent Clonic phase** → Sharp repetitive muscular jerks
        - Tongue biting, incontinence of urine, and salivation may occur.
    - When the jerking stops, patients remain unconscious for 30 mins and then are confused and drowsy for several hours.
    - **On recovery** → there is headache, stiffness or injury from fall, back pain is common, muscle spasms may be sufficient to cause vertebral fractures.
    - This type of epilepsy is controllable with one drug.
- **Partial Epilepsy**: 1- Temporal lobe epilepsy. 2- Jacksonian epilepsy.
    - **Temporal lobe epilepsy**:
        - An aura or warning of the attack may consist of psychic symptoms (fear or sensation of Déjà vu), hallucinations (olfactory, gustatory, or visual), rising sensation from the epigastrium.
        - Patients become confused and anxious and have organized stereotyped movements (automatism) including chewing and lip smacking.
    - **Jacksonian epilepsy**:
        - Begin in the corner of the mouth, the thumb and index finger, or the great toe.
        - Movements rapidly spread across the face or ascend the limb (Jacksonian march).
        - Associated with organic brain disease; tumor in the region of motor cortex.
        - After the attack, the affected limb remains temporarily weak → **Todd's paralysis**.

        - **Epilepsia Partialis Continua**: a rare form of Jacksonian epilepsy, where the attack persists for days, weeks or months.
- **Important Epileptic syndromes of childhood and adolescence**: 1- Febrile convulsions. 2- Infantile spasms (West's syndrome). 3- Absence epilepsy (petit mal). 4- Juvenile myoclonic epilepsy (Janz syndrome).
    - **Febrile convulsions**:
        - Seizures associated with fever.
        - Occur in children, 3 months to 5 years.
        - Brief (< 15 mins), generalized, some children have focal prolonged attacks with residual neurological signs.
        - Isolated attack without recurrence in 70% of the cases.
        - Carry a risk of subsequent epilepsy in 2-5% of the cases.
        - Doesn't require treatment.
    - **Infantile spasms (West's syndrome)**:
        - **A triad of**: 1- brief spasms beginning in the first few months of life (shock like flexion of the arms, head and neck with drawing up of the knees – salaam attacks-). 2- progressive learning difficulties. 3- characteristic EEG abnormality (hypsarrhythmia).
        - Could be **idiopathic** or **due an identified cause**: 1- perinatal asphyxia. 2- encephalitis. 3- metabolic disorders. 4- cerebral malformations.
        - Most conventional anticonvulsants are ineffective (though Sodium valproate and Vigabatrin may be beneficial).
        - **Treatment of choice**: Corticosteroids.
    - **Absence epilepsy (Petit mal)**:
        - Starts in childhood (4-8 years, commoner in girls), though there is also juvenile form.
        - The attacks occur without warning, the child stares blankly into space and stops talking, the eyes may flutter or roll up under the lids.
        - Recovery within seconds and may be many attacks daily.
        - Patients may develop other seizure types.
        - **Treatment**: Sodium valproate or Ethosuximide or Both.

- **Juvenile myoclonic epilepsy (Janz syndrome)**:
  - Increasingly recognized as a common form of primary generalized epilepsy, age of onset in the teens.
  - **Triad of:** 1- infrequent generalized seizures often on waking. 2- daytime absences. 3- sudden, shock like involuntary jerking movements (myoclonus) usually in the morning.
  - **Kellogg's epilepsy** → patients may inexplicably spill their breakfast or throw it across the room.
  - EEG shows polyspike-wave discharges and photosensitivity.
  - **Treatment**: 1- Sodium valproate (recurrence is likely if medication stopped). 2- Alternatives (Clonazepam, Levetiracetam, Lamotrigine).
  - Recognition of this disorder is important, as patients treated incorrectly with carbamazepine rather than valproate may worsen.

- **Diagnosis**:
  - Primarily clinical based on the description of the seizure from a witness.
  - The most important differentials are syncope and pseudo-seizure.
  - **Aims of investigations**: 1- confirming or supporting clinical diagnosis. 2- classifying the epileptic syndrome. 3- establishing the cause.
  - **Investigations**: 1- EEG. 2- Routine blood tests. 3- Brain imaging (CT / MR)
  - **EEG**:
    - Has a role in the first 2 aims especially in children (in adults there are frequent false positives and false negatives).
    - The yield can be increased by prolonged recordings particularly after sleep deprivation.
    - Ultimate proof of the diagnosis is obtained by ambulatory EEG or telemetry with simultaneous video recording of symptomatic events.
  - **Routine blood tests**:

        - Serum glucose and calcium → achieve the third aim (establishing the cause)
    - **Brain imaging**:
        - Indicated in epilepsy of later onset, presenting as partial attacks with or without focal neurological signs and EEG abnormalities.
- **Management**:
    - **Drug Management**:

Seizure type	Drugs of choice
Partial	Carbamazepine Sodium valproate Phenytoin Lamotrigine
Absence	Ethosuximide Sodium valproate Lamotrigine
Myoclonic	Sodium valproate Clonazepam Lamotrigine
Generalized tonic-clonic	Sodium valproate Phenytoin Carbamazepine Lamotrigine

        - Drug treatment is usually introduced after the second attack.
        - The choice of the drug depends on the type of the seizure.
        - Careful outpatient monitoring to establish the minimum effective dose and monitor side effects.
        - Most patients will be adequately controlled with a single drug (monotherapy).
        - Patients on >= 3 medications are less likely to have successful medical treatment.

- **Reasons for refractory epilepsy**: 1- non-concordance with meds. 2- pseudo-seizure or non-epileptic attack. 3- associated structural brain disease. 4- alcohol and lifestyle.
- **The decision to stop treatment is determined by**: 1- duration of remission. 2- type of epilepsy. 3- effect of recurrence on driving and employment. 4- side effects of meds.

			Side effects	
Drug	**Mode of action**	**Pharmacokinetics**	**Dose-related**	**Allergic**
Carbamazepine	'Membrane stabilizer' Limits repetitive firing of action potentials	Initial low dosage Controlled-release preparation permits twice-daily regime Blood levels limited value	Giddiness Nausea Drowsiness	Rashes Leucopenia
Sodium valproate	Uncertain – multiple	Controlled-release preparation permits twice-or even once-daily regime Blood levels little value	Tremor Confusion Chronic toxicity: alopecia, weight gain	Hepatitis
Phenytoin	'Membrane stabilizer'	Once-daily regime Narrow therapeutic range Blood levels useful	Drowsiness Ataxia Chronic toxicity: gum hypertrophy, acne, hirsutism, coarsening of facial features, folate deficiency	Rashes Lymphadenopathy
Lamotrigine	'Membrane stabilizer'	Half-life prolonged by sodium valproate Dosing schedule depends on concomitant drug treatment	Nausea Dizziness Tremor Headache	Rash Fever Arthralgia Lymphadenopathy Eosinophilia Stevens–Johnson syndrome

- **Surgical treatment**:

- Patients with intractable epilepsy, refractory to medical treatment are considered for neurosurgical procedures, especially those with definable site of seizure onset.
- **Surgical options include**: 1- selective removal of epileptogenic tissue. 2- hemispherectomy and disconnection procedures.

- **Other aspects**:
  - Avoid alcohol.
  - Some patients may have attacks provoked by flickering light (TV or computer screens).
  - Dietary treatment; ketogenic diet, of unproven benefit.

Older anti-epilepsy drugs retaining specific uses:

Phenobarbitone (and primidone)
Many patients with long-standing epilepsy remain on these drugs
Primidone is metabolized to phenobarbitone
Withdrawal seizures are likely if phenobarbitone is stopped abruptly
Phenobarbitone retains a role in the management of status epilepticus (Chapter 20)

Ethosuximide
Used in childhood absence epilepsy (petit mal)
May exacerbate tonic–clonic seizures

Clonazepam
Effective in myoclonic and absence epilepsy
May be administered intravenously in status epilepticus

Clobazam
Add-on therapy in tonic–clonic and partial seizures, especially if perimenstrual

Newer drugs used predominantly as add-on therapy for partial seizures:

Vigabatrin
Also used as monotherapy for infantile spasms (West's syndrome)
Avoid in patients with a psychiatric history
Associated with irreversible peripheral visual field defects in about one-third of patients
For this reason nowadays only used in exceptional circumstances outside the context of West's syndrome

Gabapentin
Also used in the management of neurogenic pain
Unlike many other anti-epilepsy drugs is eliminated by the renal route rather than hepatic metabolism

Topiramate
Also used as adjunctive treatment for primary generalized tonic–clonic seizures
Avoid in patients with a history of renal stones

Tiagabine

Oxcarbazepine
Similar indications to carbamazepine, probably has a better side effect profile

Levetiracetam
Increasingly used as monotherapy
May cause behavioural and mood change

Pregabalin
Useful in patients with epilepsy and generalized anxiety disorder

Zonisamide
Risk of renal calculi

Lacosamide

CHAPTER 11: STROKE

- **Stroke**: a syndrome consisting of rapidly developing signs and symptoms of loss of focal (or global) CNS function – lasting >24 hours or leading to death-.
- **Vascular events** → 1- Infarction (embolic / thrombotic). 2- Hemorrhagic.
- **TIA**: a rapid loss of focal CNS function, lasting <24 hours and caused by embolic, thrombotic or hemodynamic vascular mechanism.
- Some TIAs last >24 hours but patients recover completely → reversible ischemic neurological defect
- The third most common cause of death in developed countries after heart diseases and cancer.
- **The majority of strokes are cerebral infarcts**.
- **Infarction of the CNS:**
    - *Etiology and pathogenesis*:
        - Thrombosis of arteries or veins of the CNS caused by one or more of Virchow's triad: 1- abnormalities of the vessel wall (degenerative diseases, Inflammation -vasculitis-, trauma -dissection-). 2- abnormalities of the blood. 3- disturbance of the blood flow.
        - Embolism is either a complication of degenerative diseases of the arteries to the CNS or arising from heart disease (valvular disease, A fib, recent MI).
        - The most common cause of stroke is Degenerative arterial disease (Atherosclerosis in large vessels / Small vessel disease – lipohyalinosis-)
    - *Pathophysiology*:
        - Reduction of blood supply to an area of the CNS due to arterial occlusion as a result of a thrombus or an embolus leading to infarction of that area.
        - Around that necrotic area there is an Ischemic Penumbra which remains viable for a time and may recover normal function if blood flow is restored.

        - CNS ischemia may be accompanied by swelling due to: 1- Cytotoxic edema (accumulation of water in damaged glial cells and neurons). 2- Vasogenic edema (ECF accumulation as a result of breakdown of BBB).
    - *Clinical features and classification*:
        - **Vascular risk factors**: 1- Age. 2- Family Hx of vascular disease. 3- HTN. 4- DM. 5- Hypercholesterolemia. 6- Smoking. 7- Alcohol. 8- OCPs. 9- Plasma fibrinogen.
        - **Total anterior (carotid) circulation infarct**:
            - 1- Hemiplegia (damage to the upper part of corticospinal tract). 2- Hemianopia (damage to optic radiation). 3- Cortical defects; dysphasia (dominant hemisphere), visuo-spatial loss (non-dominant hemisphere).
        - **Partial anterior circulation infarct**:
            - Two of the above OR cortical defect alone.
        - **Lacunar infarct**:
            - Intrinsic disease (lipohyalinosis) in a small deep perforating artery producing a characteristic syndrome (pure motor or sensory stroke, or ataxic hemiparesis).
            - Multiple lacunar infarcts may produce cumulative neurological defects including cognitive impairment (multi-infarct dementia) and gait disorders (small steps and difficulty starting walking – gait apraxia-).
        - **Posterior (vertebrobasilar) circulation infarct**:
            - 1- Evidence of brainstem lesion (vertigo, diplopia, altered consciousness). 2- Homonymous hemianopia.
        - **Spinal cord infarction**.
    - *Investigations and diagnosis*:
        - **Common investigations**: 1- CBC and ESR. 2- Urea, Electrolytes, Glucose and Lipids. 3- Chest radiograph and ECG. 4- CT cranial scan (helps distinguish between hemorrhagic and infarction stroke which aids early management, also excludes other diagnoses).

- *Complications and course*:
  - Severely affected patients are prone to complications that may lead to early death: 1- pneumonia (aspiration pneumonia), septicemia (via pressure sores or urinary tract infection). 2- DVT and PE. 3- MI, arrhythmias, Heart failure. 4- Fluid imbalance
  - ~ 30% of patients die in the first 30 days, ~50% of survivors remain dependent.
  - **Factors contributing to long term disability**: 1- Pressure sores. 2- Epilepsy. 3- Recurrent falls and fractures. 4- Spasticity with pain, contractures, and frozen shoulder. 5- Depression.
- *Treatment*:
  - **Acute management**:
    - Admission to a stroke unit.
    - Aspirin 300mg daily
    - Thrombolysis: with IV tissue plasminogen activator (alteplase), should be started within 3 hours of stroke onset (as early as possible to minimize permanent brain injury.
      - The key steps: 1- rapid transfer to hospital. 2- rapid clinical assessment including CT to exclude intracranial hemorrhage.
      - Patients are ineligible for thrombolysis if there is uncertainty about the exact time of stroke onset or if they have risk factors for intracranial or systemic hemorrhage.
    - Surgery is rarely needed in acute management (posterior fossa decompression and ventricular drainage if swelling is leading to brainstem compression and obstruction to CSF flow).
      - **Malignant MCA occlusion syndrome**: young patients with total MCA infarction may develop massive cerebral edema with high risk of raised ICP, brainstem compression and death →

temporary removal of the skull vault on the side of the infarct (hemicraniotomy).

- *Prevention*:
  - 1- Modifying risk factors (stopping smoking and manipulating diet). 2- Prescribing cholesterol lowering agents (statins). 3- control of BP. 4- lifelong antiplatelet treatment (aspirin 300 mg daily, reduced to 75 mg daily after 4 weeks). 5- anti-coagulation with warfarin in the case of A fib or other cardiac sources of emboli.
  - In the first 2 weeks, patients shouldn't receive any antihypertensive therapy beyond their pre-existing treatment unless there is evidence of malignant HTN → as too rapid lowering of BP may worsen ischemia in the region where the cerebral circulation is already compromised.

- *Hypotension and Hypertension*:
  - Cerebral blood flow is normally maintained at constant level (80-180 mm Hg systolic) through autoregulation.
  - If blood pressure falls below the autoregulatory range , as with hypovolemic shock, cerebral infarction may result as blood vessels are unable to dilate further in response to drop in pressure, affecting mostly the border zones or watersheds between vascular territories.
  - With severe (malignant) HTN, the autoregulatory range may be exceeded and cerebral blood flow rises with damage to the vessel walls (fibrinoid necrosis) and consequent cerebral edema. Patients develop features of raised ICP (headache, vomiting, drowsiness, and papilledema) along with seizure and focal neurological signs.
  - Treatment of hypertensive encephalopathy is by prompt lowering of the blood pressure aiming at a diastolic pressure of 100-110 mm Hg initially.
- *Venous Infarction*:

        - **Superior sagittal sinus thrombosis presents with**: 1- Headache, papilledema and other features suggestive of idiopathic intracranial HTN. 2- Early seizure. 3- Bilateral signs of neurological defects, often progressive with impairment of consciousness.
        - **Causes**: 1- puerperium. 2- dehydration. 3- cachexia. 4- coagulopathies. 5- OCPs.
        - **Cavernous sinus involvement** produces red swollen eyelid and conjunctiva, III, IV, VI, Va and Vb cranial nerve palsies and papilledema.
        - **Lateral sinus involvement** produces raised ICP, seizures and drowsiness.
            - Those 2 sinuses may undergo thrombosis as a result of spread of infection from the face and orbit to the cavernous sinus and from the ear to the lateral sinus.
        - **Treatment**: aimed at the underlying cause → 1- Eradicating infection with appropriate antibiotic. 2- Formal IV heparinization (for non-infectious cases).
- **Transient Ischemic attacks**:
    - *Etiology*:
        - Most commonly caused by thromboembolism from atheromatous neck vessels.
        - Other causes: 1- Lipohyalinosis of intracranial small vessels. 2- Cardiogenic embolism. 3- Vasculitis or hematological diseases.
    - *Clinical features*:
        - The hallmark is sudden loss of focal CNS function.
        - TIAs typically last minutes not hours, and the arterial territory of the attack will determine the symptoms.
        - **Carotid** (most commonly):
            - Hemiparesis, Hemisensory loss, Dysphasia, Monocular visual loss (amaurosis fugax) caused by retinal ischemia.
        - **Vertebrobasilar**:

        - Bilateral or alternating paresis or sensory loss, Bilateral sudden visual loss, Diplopia – Ataxia – Vertigo – dysphagia (at least 2 of these simultaneously).
    - Neurological signs are usually absent by the time the patient is seen by the doctor, but cholesterol emboli may be visible on ophthalmoscopy in patients with amaurosis fugax.
    - A carotid bruit may be audible.
    - Cardiac arrhythmias and murmurs may point to a cardiac source of embolism.
    - **Subclavian Steal syndrome**: a rare cause of vertebrobasilar TIAs, in which stenosis of the subclavian artery may lead to retrograde flow down the vertebral artery when the arm is exercised.
- *Investigations and diagnosis*:
    - **DDx**: 1- migraine with aura. 2- Partial epilepsy. 3- intracranial tumor, vascular malformation, chronic subdural hematoma. 4- MS. 5- vestibular disorders. 6- peripheral nerve or root lesion. 7- hypoglycemia. 8- hyperventilation and other psychogenic processes.
    - The recognition of TIAs depends on the Hx.
    - **Investigations** (directed toward identifying the cause and preventing more serious complications): 1- CBC, ESR. 2- Blood glucose and cholesterol. 3- Syphilis serology. 4- ECG. 5- Chest radiographs, Echo, 24-hour ECG (when cardiogenic embolism is suspected). 6- CT cranial scan (to detect pre-existing cerebrovascular disease + exclude structural lesions). 7- Carotid US or angiography (to detect carotid stenosis). 8- Blood cultures (when infective endocarditis is suspected).
- *Prognosis and treatment*:
    - The risk of stroke in the first 5 years after a TIA is ~ 7% per annum, with the greatest risk being in the first year.
    - Increased risk of MI after TIA.

        - High risk patients should be assessed within 24 hours of the event, Low risk patients within a week.
        - **Preventive measures:** 1- Modifying risk factors (treat HTN, Stop smoking, reducing serum cholesterol by diet and drugs). 2- Antiplatelet drugs (low dose aspirin; contraindicated in active PUD; combined aspirin and dipyridamole is more effective than either agent alone; clopidogrel is an alternative for patients who can't tolerate aspirin). 3- Anticoagulants (warfarin; when cardiogenic emboli has been identified). 4- Carotid endarterectomy (surgical intervention to clear atheroma from the origin of internal carotid artery).
- **Subarachnoid hemorrhage**:
    - *Etiology*:
        - Bleeding into the subarachnoid space from:
            - 1- Rupture of an aneurysm (congenital weaking at the junctions of the circle of Willis). 2- AV malformation (angioma). 3- Trauma. 4- Vessels weakened by infection (septic emboli from infective endocarditis – mycotic aneurysm-). 5- Coagulopathies
    - *Clinical features*:
        - Sudden very severe headache with photophobia, nausea, vomiting and signs of meningism (neck stiffness and Kernig's sign) → as blood irritates the meninges.
        - Raised ICP and the level of consciousness deteriorate.
        - Papilledema and retinal hemorrhages may be detected on fundoscopy.
        - Focal neurological signs as a result of: 1- false localizing sign due to raised ICP. 2- coexistent intracerebral hemorrhage. 3- spasm of vessels as a result of irritant effect of blood.
        - Systemic features including: Bradycardia, Hypertension with raised ICP, Fever (caused by hypothalamic damage), Pulmonary edema, Cardiac arrhythmia.
    - *Investigations*:

        - CT scan, small bleeds may not be detected on CT → Lumbar puncture (contraindicated in the case of mass lesion), Chest radiograph and ECG (for pulmonary edema and cardiac arrhythmias), Bleeding disorders should be excluded, Glycosuria is sometimes present.
        - Lumbar puncture shows frank blood that fails to clear + CSF supernatant is straw or yellow colored (xanthochromia) within 3 hours of the hemorrhage due to hemoglobin breakdown products.
    - *Prognosis and management*:
        - Aneurysmal subarachnoid hemorrhage carries a risk of mortality (30-40% dying in the first few days).
        - Significant risk of rebleeding in the first 6 weeks with the second bleed being more severe than the first.
        - **Management**:
            - Bed rest and analgesia.
            - Calcium antagonist Nimodipine.
            - Operative techniques including clipping the aneurysmal neck or wrapping the aneurysm.
        - **Early complications**: 1- Hydrocephalus (due to obstruction of CSF pathways by blood clot) → Communicating hydrocephalus later.
        - Bleeding AV malformations have lower mortality than aneurysm → surgical treatment.
- **Spontaneous intracerebral hemorrhage**:
    - Hemorrhage into the substance of the brain caused by: 1- HTN with microaneurysm formation (Charcot Bouchard aneurysm). 2- Bleeding into a tumor. 3- Trauma. 4- Blood disorders. 5- Blood vessels disorders (AV malformations, Vasculitis, Amyloid).
    - Patients present with focal neurological signs depending on the site of bleed + Seizures + Features of raised ICP.
    - **Diagnosis** → CT scan.
    - **Complications**: 1- Hydrocephalus. 2- Coning.
    - Large hematomas + brainstem hemorrhages have poor prognosis.
    - **Treatment**:

- Initially medical with 1- antihypertensive drugs. 2- anti-epilepsy drugs for seizures. 3- correction of coagulopathies. 4- mannitol for raised ICP.
- Surgical interventions: 1- evacuation of hematoma for cerebellar or cerebral lobar hemorrhage with progressive deterioration. 2- ventricular drainage for acute hydrocephalus.

CHAPTER 12: PARKINSON DISEASE AND OTHER MOVEMENT DISORDERS

- **Parkinson's disease**: a degenerative condition primarily affecting extrapyramidal pathways where dopamine is a neurotransmitter.
- A **triad** of: 1- Tremor (shaking back and forth mostly in the upper limb). 2- Rigidity. 3- Akinesia.
- **Etiology**:
    - Unknown cause.
    - MPTP (a synthetic heroin by-product) could produce acute parkinsonism
    - Parkinson's disease may be caused by exposure to widely prevalent environmental factors perhaps acting by a similar mechanism to MPTP.
    - The disease is increasingly common with age (mean age ~ 60 yrs).
    - Genetic causative factors have been identified (positive family Hx is relatively unusual in idiopathic Parkinson's).
    - Weak association between Parkinson's and various environmental factors.

Table 12.1 Causes of an akinetic–rigid syndrome.

Inherited
Wilson's disease – Chapter 18

Traumatic
'Punch-drunk syndrome' – chronic head injury in boxers – patients have parkinsonian features often in combination with cerebellar damage and cognitive deficits (dementia pugilistica)

Inflammatory
Postencephalitic Parkinsonism – following the epidemic of encephalitis lethargica after World War I, patients developed a chronic akinetic–rigid state, with certain characteristic features, particularly oculogyric crises (see text)

Neoplastic
Tumours of the basal ganglia presenting with contralateral hemiparkinsonism are extremely rare

Vascular
Multiple lacunar infarcts may occasionally result in pseudoparkinsonian features, but usually in association with pyramidal and cognitive dysfunction

Drugs
Neuroleptics
Antiemetics
Amiodarone

Toxins
MPTP
Manganese
Chronic carbon monoxide poisoning

Idiopathic
Parkinson's disease
(Other idiopathic syndromes are listed in Table 12.2)

- **Epidemiology**:
  - Common disease.
  - 1-2% of population aged 60+ years.
  - No significant gender bias.
  - More common in Europe and North America.
- **Pathology**:
  - The dopaminergic neurons primarily affected are those projecting from substantia nigra of the midbrain to the striatum of the basal ganglia (caudate nucleus and putamen).
  - Macroscopically, atrophy of substantia nigra is recognizable by loss of the characteristic melanin pigmentation of this region.
  - Microscopically, severe neuronal loss is demonstrable in the substantia nigra, remaining neurons often containing a distinctive intracellular inclusion (Lewy bodies)
  - Symptoms appear when ~ 60-70% of nigrostriatal dopaminergic neurons have been lost.
  - Damage to dopaminergic pathways leads to an imbalance in the extrapyramidal system in favor of cholinergic and other neurotransmitter mechanisms.

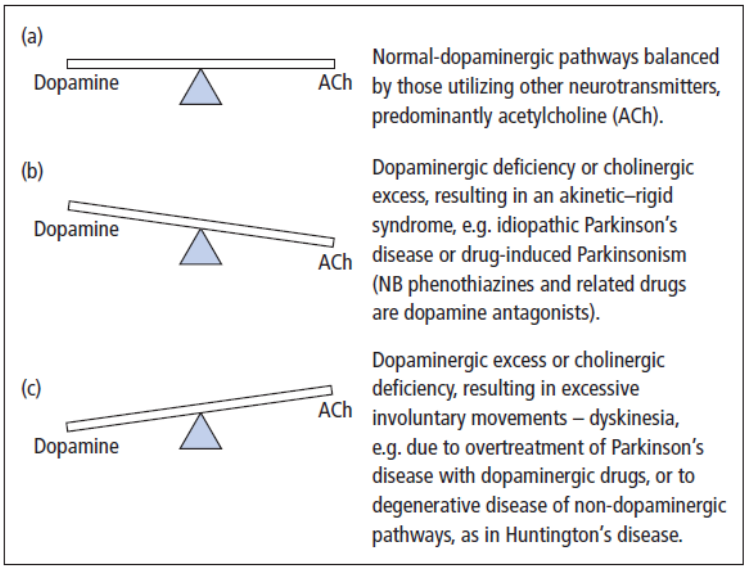


Figure 12.4 The concept of neuro-chemical balance in the extrapyramidal system.

- **Clinical features**:
  - *Akinesia*:

        - Patients may complain from being ‘slowed down’ physically → Bradykinesia, experiencing particular difficulties with complex motor tasks; dressing, shaving, handwriting (micrographia).
        - Poverty of facial expressions (mask-like face).
        - Difficulty changing position.
        - Quiet and monotonous speech.
        - Abnormal gait and stance (partly as a consequence of akinesia and partly because of loss of normal postural control).
    - *Gait*:
        - Patients adopt a flexed or stooped posture (Simian or apelike).
        - Unable to maintain normal stance in response to pressure from behind, the patient falling forward (Propulsion), or from in front, falling backwards (Retropulsion).
        - Initiation of walking may be difficult (freezing).
        - Steps are small and shuffling the gait described as festinant (as if the patient is hurrying to keep up with his/her own center of gravity).
        - Loss of normal arm swing on walking, with severe postural instability in advanced disease.
        - Increased risk of falls.
    - *Rigidity*:
        - Increased muscle tone, which is constant throughout the range of movement of the joint being tested (lead pipe rigidity).
        - Cogwheel rigidity → as a consequence of the tremor, more frequently detected with repeated flexion and extension, or rotation at the wrist.
    - *Tremor*:
        - Involuntary, repetitive, rhythmic sinusoidal movement usually affecting one or more limbs, occasionally involving the head (titubation), face, jaw or trunk.

- In Parkinson's the tremor 1- primarily affect the hands but may involve upper and lower limbs and less frequently the jaw and lips, but not the head or neck. 2- In the hands described as 'pill rolling'. 3- Present at rest and exacerbated by anxiety and stress. 4- Improves and may disappear on action.
- Early in the disease, tremor and other physical signs are typically markedly asymmetrical, even unilateral.
- A minority of patients with Parkinson's display only akinesia and rigidity without tremor. Other patients may have postural tremor rather than a classical resting tremor.

- *Other motor signs and symptoms*:
  - **Cranial nerves**:
    - Mild impairment of the upgaze.
    - The eyelids may be tremulous (blepharoclonus).
    - Glabellar tap sign → elicited by repeated taps to the forehead, in unaffected individuals, reflex blinking rapidly fatigues, whereas in Parkinson's there is a blink response each time the forehead is touched without fatigue (however it's not specific for Parkinson's).
  - **Difficulty swallowing, resulting in tendency to drool → sialorrhea**.
  - **Limbs**:
    - Muscle power, tendon reflexes and sensation are normal.
    - Planter reflexes are down-going.
    - Pain or aching in muscles (many patients present with or develop a 'frozen shoulder').
- *Non-motor symptoms*:
  - Depression
  - Hallucinations: vivid, formed visual hallucinations may occur particularly at night.

        - Psychosis: worsening hallucinations and delusions may escalate to full-blown psychosis, particularly in patients who also have cognitive impairment.
        - Dementia
        - Sleep disorders: Insomnia is common and may relate to immobility, mood disturbances, hallucinations and various sleep-related behavioral and movement disorders.
        - Autonomic symptoms: 1- the skin may have greasy seborrheic texture. 2- Constipation. 3- bladder disturbances and erectile dysfunction. 4- postural hypotension.
        - Anosmia
- **Course and prognosis**:
    - Progressive and divided into 3 stages: 1- **Early**; when symptom control is good. 2- **Mid**; when motor fluctuations and dyskinesia develop. 3- **Late**; when treatment resistant features such as dementia and falls occur.
    - Untreated patients used to reach a severely disabling degree of immobility with a threat to life from bronchopneumonia, septicemia, or pulmonary embolus.
- **Diagnosis**:
    - The diagnosis is based on the presence of the triad of the clinical features, asymmetry of the signs at the onset is important.
    - CT and MRI are unhelpful.
    - Where the diagnosis is in doubt, a patient's response to drug treatment may be informative.
    - A lack of response to antiparkinsonian treatment is an important discriminant between Parkinson's and other idiopathic akinetic-rigid syndromes.
- **Treatment**:
    - *Drug therapy*:
        - Largely symptomatic treatment and aimed at restoring the neurochemical balance either by anticholinergic agents or with drugs that enhance the dopaminergic pathway.
        - Treatment is best delayed until symptoms warrant it.
        - **L-Dopa**:

- The mainstay of drug treatment for Parkinson's disease severe enough to cause significant functional disability.
- Unlike dopamine, L-dopa can cross BBB, thus can reach its site of action following oral administration.
- Most of the oral dose is metabolized to dopamine by peripheral Dopa decarboxylase before reaching the brain; so it's given in combination with a peripheral Dopa decarboxylase inhibitor (Carbidopa, Benserazide), it also reduces the peripheral side effects of L-dopa (nausea, vomiting).
- **Co-careldopa** (L-Dopa plus carbidopa) **and Co-beneldopa** (L-Dopa plus benserazide) may have central side effects (postural hypotension, confusion, hallucinations, and delusions).
- **Complications of long-term L-Dopa therapy**:
    - After 2-5 years, the efficacy of L-dopa becomes limited by motor fluctuations and dyskinesia.
    - **Motor fluctuations**: 1- Wearing-off (where individual doses produce only short-lived effects. 2- On-Off (the patient switches from symptomatic benefit from medication (on) to an akinetic-rigid state (off), often without any predictable relationship to the timing of drug doses.
    - **Dyskinesia**: involuntary movement occurring in association with drug treatment (twisting and turning movements) when dopamine levels are high (Peak-dose dyskinesia), or painful sustained muscle contractions, typically of the feet when dopamine levels are low (Wearing-off dystonias).
    - **Dopamine dysregulation syndrome**: high levels of L-Dopa above that required for motor

function resulting in bizarre, repetitive, compulsive behavioral disturbances.

- **Motor fluctuations and dyskinesias are alleviated in some patients** by: 1- frequent small doses of L-Dopa containing drugs. 2- controlled release preparations. 3- the combined use of L-dopa containing preps with A- Selegiline (MAO-B inhibitor) which blocks dopamine metabolism. B- Entacapone (COMT inhibitor). C- Direct dopamine receptor antagonist. 4- attempts to mimic physiological dopamine level by continuous administration of L-Dopa or dopamine agonists (transdermal administration of rotigotine – a dopamine agonist-, subcutaneous infusion of apomorphine, and duodenal infusion of L-dopa). 5- surgery.

- Other side effect of L-dopa can be treated by drugs with least central dopamine antagonist action, Domperidone for nausea, atypical narcoleptics such as Risperidone, Olanzapine, Clozapine.

- **Other drugs**: 1- Selegiline (MAO-B inhibitor). 2- Rasagiline (MAO-B inhibitor). 3- Dopamine agonists (bromocriptine, cabergoline, pergolide; these drugs play a major role in early Parkinson's, potentially delaying the need for L-Dopa). 4- Amantadine (only mildly beneficial in early Parkinson's, it later can reduce L-Dopa induced dyskinesias only for a limited period). 5- Anticholinergic drugs (Trihexyphenidyl, Orphenadrine, Benztropine; help tremor against which L-Dopa preps are less useful).
- Bromocriptine, Cabergoline and Pergolide are derived from Ergot and thus are associated with pulmonary and retroperitoneal fibrosis.
- Up to 1/3 of patients on pergolide develop fibrotic cardiac valvulopathy.

        - Non-ergoline dopamine agonists (ropinirole, pramipexole) are preferred nowadays.
        - **Ropinirole and Pramipexole side effects**: 1- excessive drowsiness. 2- sudden onset of sleep without warning. 3- bizarre behavioral disturbances.
        - **Anticholinergics side effects**: 1- urinary retention. 2- dry mouth. 3- blurry vision. 4- confusion and hallucinations.
    - *Surgical treatment*:
        - **Stereotactic thalamotomy**: infrequently used with improved drug therapy, useful in patients with severe tremor unresponsive to medications.
        - **Cell transplantation using fetal substantia nigra**.

- **Other movement disorders**:
    - *Chorea*:
        - Irregular, random, and variable movements, but have flowing or dancing quality which may appear semipurposeful.
        - **Causes of acquired chorea**: 1- Chronic L-Dopa therapy in Parkinson's disease. 2- Postinfectious (Sydenham's chorea in association with Rheumatic fever). 3- Polycythemia rubra vera. 4- SLE. 5- Thyrotoxicosis. 6- Pregnancy and OCPs. 7- Phenytoin, alcohol, neuroleptics.
        - Hereditary chorea is seen in Huntington's disease in association with dementia.
        - Chorea may respond to the Monoamine depleting drug **Tetrabenazine**, but it may produce severe depression. Alternatives include **neuroleptics**; sulpiride, haloperidol.
        - In **Hemiballismus**: movements are more violent and jerky and are restricted to one part of the body, occurring as a result of damage to the contralateral subthalamic nucleus.
    - *Athetosis*:
        - Movements are slower and more writhing than chorea.
        - It represents the transition from one dystonic posture to an another.

- Associated with congenital brain damage; cerebral palsy, particularly the one used to occur with neonatal hyperbilirubinemia.

- *Tremor*:

Table 12.3 Causes of tremor.

Rest tremor
Parkinson's disease
Other akinetic–rigid syndromes
Postural tremor (maximal with maintained posture)
Essential tremor
Physiological tremor; may be exaggerated by:
Anxiety
Thyrotoxicosis
Alcohol
Drugs, e.g. bronchodilators
Kinetic tremor (i.e., during movement, often worse as a target is approached – intention tremor)
Cerebellar diseases:
Multiple sclerosis
Hereditary ataxias
Tumour, infarct or haemorrhage of the cerebellum
Postural and kinetic tremors may be associated with dystonia, and with some peripheral neuropathies

  - **Essential tremor**: 1- positive family history. 2- postural tremor of both hands, hence difficulty holding cups, writing. But other body parts including the head may be affected. 3- tremor absent at rest. 4- no extrapyramidal or cerebellar clinical features. 5- may be relieved by alcohol. 6- may respond to treatment with Propranolol or Primidone.
  - **Primary orthostatic tremor**: unsteadiness or tremor in the legs brought on by prolonged standing. Clonazepam may be helpful.

- *Dystonia*:
  - Involuntary sustained muscle contractions resulting in abnormal postures.
  - May be:
    - **Focal**: 1- Blepharospasm (involuntary eye closure). 2- Oculogyric crises (eyes rolled upwards). 3- Spasmodic torticollis (painful contractions in sternomastoid resulting in head being turned involuntarily to one side, also sometimes forward -antecollis- or backwards -retrocollis-) 4- Laryngospasm. 5- Trismus (jaw spasm). 6- Writer's cramp (painful abnormal

posture of the hand stopping the patient from writing).
        - **Generalized**: as in the inherited condition of **Primary torsion dystonia**. Also seen in drug reactions and as a symptom of many causes of cerebral damage.
    - Drug treatment is unsatisfactory, though generalized dystonias may respond to increasing doses of anticholinergic agents.
    - **Focal dystonias** treated successfully with injection of the affected muscles with **Botulinum toxin**.
    - **Rare paroxysmal dystonias** may respond to **anti-epilepsy drugs**.
- *Myoclonus*:
    - Rapid, abrupt, jerky, shock like movements of part or the whole body, which may occur in the context of abnormal electrical discharges of the cerebral cortex (with epilepsy).
    - May arise from elsewhere in the CNS.
    - **First line drugs**: Sodium Valproate, Clonazepam.
- *Tics*:
    - Rapid compulsive repetitive, stereotyped movements, AKA habit spasms.
    - Can be voluntarily resisted for a limited period, but often is more violent immediately after resistance has been abandoned.
    - Drug treatment is difficult, but patients may respond to **neuroleptics**.

- **Drug induced movement disorders**:
    - *Neuroleptic drugs* (through dopamine receptor antagonist action):
        - 1- Acute dystonic reaction. 2- Akathisia (restlessness). 3- Drug induced parkinsonism. 4- Tardive dyskinesia (involuntary movements in the face and mouth which may persist after the drug has been discontinued).

        - The most severe disorder associated with these drugs → **Neuroleptic malignant syndrome**: patients have generalized muscular rigidity and fever in association with tremor, incontinence, altered consciousness, cardiovascular changes, muscle damage with elevated CK and sometimes myoglobinuria.
        - **Treatment of Neuroleptic malignant syndrome**: 1- resuscitation and withdrawal of the offending agent. 2- Dopamine receptor agonist (bromocriptine). 3- muscle relaxant (dantrolene).

- **Miscellaneous movement disorders**:
    - *Restless leg syndrome*:
        - Distressing irresistible desire to move the legs (akathisia), associated with an uncomfortable deep-seated sensation in the legs, worse in the evening or night.
        - Symptoms brought on by rest and relieved by movement.
        - May be associated with: 1- peripheral neuropathy. 2- lumbar root disease. 3- IDA. 4- renal failure.
        - **First line drugs**: dopaminergic agents, either dopamine receptor agonist or L-Dopa.
        - **Other drugs**: Opiates, Clonazepam, Gabapentin, and Iron replacement therapy
    - *Stiff person syndrome*:
        - Slowly progressive rigidity in the trunk and proximal limbs with superimposed painful muscle spasms.
        - associated with DM and Epilepsy.
        - **Diagnosis**: EMG findings + Specific autoantibodies and oligoclonal bands in CSF.
        - **Treatment**: immunomodulatory agents such as Steroids, IVIG, Plasma exchange, + Benzodiazepines.

CHAPTER 14: NEUROLOGICAL INFECTIONS.

- **Bacterial (Pyogenic) meningitis**:
  - *Etiology*:
    - Caused by infection of the meninges by: 1- Neisseria meningitides. 2- Streptococcus pneumoniae.
    - Others: Mycobacterium TB; mainly in immunocompromised. Haemophilus influenzae type b (rarer after the introduction of the vaccine).
  - *Epidemiology*:
    - Meningococcal meningitis may occur in epidemics.
    - Pneumococcal infection is common in elderly and is associated with alcoholism and splenectomy. It may spread to the meninges from adjacent structures (ears and nasopharynx) or from the lungs by blood stream.
  - *Clinical features*:
    - Severe headache associated with pain and stiffness in the neck and the back + vomiting and photophobia + altered level of consciousness and seizures.
    - Rapid onset, though not as sudden as subarachnoid hemorrhage.
    - Signs of infection: 1- fever. 2- tachycardia. 3- shock. 4- evidence of the primary source of infection (pneumonia, endocarditis, sinusitis, otitis media).
    - **Rash in all patients with meningococcal meningitis** (petechial or purpuric).
    - Neurological signs:
      - **Meningism**: neck stiffness on attempted flexion + high-pitched meningeal cry in infants + Kernig's sign.
      - **Deteriorating level of consciousness**.
      - **Raised ICP**: papilledema + bulging fontanelle in infants.
      - **Cranial nerve palsies**.
  - *Investigations and diagnosis*:

        - **Lumbar puncture**: 1- turbid CSF. 2- raised CSF pressure. 3- polymorph leukocytosis (hundreds or thousands of cells per μL). 4- raised protein concentration (>1g/L). 5- low glucose concentration (mostly undetectable). 5- the causative organism may be identified on gram stain.
            - **Contraindications to LP**: 1- papilledema. 2- deteriorating level of consciousness. 3- focal neurological signs.
            - In such patients we should do **pre-puncture cranial CT to exclude mass lesion**.
        - **Other tests**: 1- CBC (neutrophilia). 2- Coagulation studies (disseminated intravascular coagulation). 3- Electrolytes (hyponatremia). 4- Blood cultures (may be positive even if CSF is sterile). 5- Chest and skull (sinus) radiography (to identify primary source of infection).
    - *Complications*:
        - **Acute**: 1- seizures. 2- abscess formation. 3- hydrocephalus. 4- inappropriate ADH secretion. 5- septic shock.
        - **Waterhouse-Friderichsen syndrome**: a severe manifestation of septic shock with disseminated intravascular coagulation and adrenal hemorrhage.
        - Meningococcal disease is also complicated by Arthritis (septic or immune-complex mediated).
    - *Management*:
        - Disease may be fatal within hours → early diagnosis and treatment with appropriate IV antibiotics.
        - **Drug of choice for meningococcal and pneumococcal infections**: **Benzylpenicillin**; initial dose of 2.4g then 1.2g every 2 hours. If there is improvement within 48-72 hours, relax the regimen to every 4-6 hours. Continue treatment for 7 days after the patient has become afebrile (14 days for pneumococcal).
        - **Empirical antibiotics → Cefotaxime, Ceftriaxone**. Add **ampicillin** if the patient is immunosuppressed, pregnant or elderly (to cover listeria).

        - **Vancomycin** if there is a risk of Staph aureus; like with shunt associated meningitis.
        - Patients with suspected meningococcal meningitis should be given a **single IV or IM injection of benzylpenicillin** before admission.
        - If LP is delayed for CT scan, antibiotics should be started before the scan, after the blood sample has been taken.
        - High-dose IV corticosteroids (**dexamethasone** 0.4mg/kg body weight daily for 4 days) → reduce inflammatory response.
        - **Other treatment measures**: 1- bed rest. 2- analgesics. 3- antipyretics. 4- anti-epilepsy drugs for seizures. 5- supportive measures for coma, shock, raised ICP, electrolyte disturbances and bleeding disorders.
    - *Prevention*:
        - **Chemoprophylaxis** (rifampicin / ciprofloxacin) → household contacts of meningococcal meningitis.
        - **Immunization against H. Influenza infection** (with H. Influenza type b vaccine) → children at the ages 2,3,4 months.
    - *Prognosis*:
        - Overall mortality = 10% (higher in S. pneumonia infection).
        - **Pneumococcal disease causes long-term sequelae**: 1- hydrocephalus. 2- cranial nerve palsies. 3- visual and motor deficits. 4- epilepsy.
        - **Children may be left with**: 1- behavioral disturbances. 2- learning difficulties. 3- hearing loss. 4- epilepsy.
- **Other bacterial infections**:
    - *Brain abscess*:
        - **Etiology**:
            - **May complicate otitis media** (giving rise to temporal lobe and cerebellar abscess) and other local sites of infection (paranasal sinuses).

        - Also, by distant spread from the lungs (bronchiectasis), pelvis or heart (bacterial endocarditis and congenital lesions).
    - **Clinical features**:
        - **Features of an expanding mass in the brain**: 1- raised ICP. 2- focal signs (dysphasia, hemiparesis, ataxia). 3- seizures.
        - Fever is common but doesn't always develop.
    - **Investigations**:
        - **CT scan or MRI is mandatory**.
        - **Lumbar puncture is contraindicated**.
        - **Blood tests including CBC (neutrophil leukocytosis) and blood cultures**.
    - **Management**:
        - Neurosurgical intervention to decompress and drain the abscess.
        - **Broad spectrum antibiotics** (cefotaxime + metronidazole) → until the accurate bacteriological diagnosis has been reached.
        - **Corticosteroids** (with antibiotic cover) → to treat cerebral edema.
- *Parameningeal infections*:
    - Pus accumulation in the epidural space, particularly in the spine.
    - **Most common organism**: S. aureus from a distant skin infection.
    - There may be associated osteomyelitis of the vertebrae and infection of intravertebral disks.
    - Patients present with Back pain, Fever, and Rapidly developing paraparesis.
    - **Investigations**: Spinal MRI + Blood cultures.
    - **Treatment**: Anti-Staphylococcal antibiotics + Early surgical intervention if there is evidence of neural compression.

        - **Subdural empyema**: spread of local infection of the face and scalp to intracranial subdural space and to the intracranial venous sinuses (resulting in septic venous sinus and cortical venous thrombosis).
    - *Tuberculosis*:
        - Tuberculous meningitis presents acutely than purulent bacterial meningitis.
        - **People at risk**: 1- immunocompromised. 2- certain ethnic minorities. 3- immigrant populations.
        - **Presentation**: 1- persistent headache. 2- fever. 3- seizures. 4- focal neurological signs. 5- high CSF pressure with mixed polymorphs and lymphocytes + raised protein and glucose.
        - Organisms are frequently not seen on auramine or Ziehl-Neelsen staining → bacteriological diagnosis may require multiple CSF specimens and culture + detection of mycobacterial nucleic acid by PCR.
        - **Treatment**: initially with Isoniazid (with pyridoxine cover), Rifampicin, Pyrazinamide and Fourth drug (usually ethambutol or streptomycin).
            - Anti-TB chemotherapy must be continued long term (9-12 months or more).
            - Pyrazinamide and the 4th drug may be discontinued after 2 months.
            - **Corticosteroids are used initially in combination with antituberculous drugs → to suppress inflammatory response and reduce the risk of cerebral edema.**
        - **M. tuberculosis may produce chronic caseating granuloma (tuberculoma) which act as intracranial mass lesion**.
        - Spinal TB may result in cord compression → **Pott's disease of the spine**.
        - **Other complications**: Hydrocephalus + Stroke-like event.
    - *Syphilis*:
        - Neurosyphilis is still seen among the homosexual population in the context of HIV.

- **Clinical entities**:
  - Mild self-limiting meningitis of secondary syphilis.
  - **Meningovascular syphilis**: inflammation of the meninges and cerebrospinal arteries in tertiary syphilis; present with subacute meningitis + focal signs (cranial nerve palsies, hemiparesis, paraparesis, wasting of the intrinsic hand muscles – syphilitic amyotrophy-).
  - **Gumma**: focal meningovascular disease presenting as an intracranial mass lesion.
  - **Tabes dorsalis**: parenchymatous disease primarily affecting dorsal root ganglion cells of spinal cord.
  - **General paralysis of the insane'**: parenchymatous disease of the brain.
  - **Congenital neurosyphilis**.
- **Diagnosis**: Serological tests for syphilis in blood and CSF.
  - **CSF findings**: up to 100 lymphocytes/μL + raised protein + oligoclonal bands.
- **Treatment**: IM procaine penicillin (1.8 – 2.4 g daily for 17 days) + Oral probenecid.
  - **Steroid during the initial penicillin therapy to prevent Jarisch-Herxheimer reaction** (inflammatory response to the rapid killing of spirochaetes).

- *Lyme disease*:
  - Infection with **the spirochete Borrelia Burgdorferi → transmitted by tick bite**.
  - Neurological manifestations + systemic features of the disease.
  - **Acute phase** (the first month after the bite): Meningism + fever + rash + joint pains.
  - **Chronic disease** (weeks to months after the bite): Meningitis + Encephalitis + Cranial nerve palsies (especially the facial nerve) + Spinal root and peripheral nerve lesions.
  - **Diagnosis**: serological tests.

        - **Treatment**: Cefotaxime / Ceftriaxone.
    - *Leprosy*:
        - Invasion of peripheral nerve by **Mycobacterium leprae**.
        - Tuberculoid leprosy (more benign and less infectious), causes patchy sensory polyneuropathy with palpable thickened nerves and depigmented anesthetic areas of the skin.
        - **The most common cause of multifocal neuropathy worldwide**.
    - *Bacterial toxins*:
        - **Tetanus toxin from Clostridium tetani in wound infections** → tonic spasms of the jaw and trunk, then fever with painful paroxysmal spasms of the whole body + arched back + clenched teeth + extended limbs.
            - **Treatment**: in ICU involving muscle relaxants and ventilatory support + human antitetanus immunoglobulin + penicillin + wound cleansing.
            - **Eradication with active immunization with tetanus toxoid**.
        - **Botulism**: **toxin production by Clostridium botulinum** in inadequately sterilized canned food, also seen in heroin addicts (infecting skin wounds).
            - Present with Diarrhea + Vomiting + Paralysis within 2 days of toxin ingestion (the weakness is descending in evolution).
            - Assisted ventilation is required, and recovery is very slow (months or even years).
        - **Diphtheria toxin causes polyneuropathy**; very rare in developed countries due to immunization.
- **Viral infection**:
    - *Viral meningitis*:
        - Infection with **Mumps**, **Enteroviruses**, and some other viruses.
        - Benign self-limiting illness without the severe complications of bacterial meningitis.

        - **CSF findings**: 1- raised pressure. 2- several hundred cells /µL (lymphocytes with few polymorphs except in the early stages). 3- high protein. 4- normal glucose.
    - *Viral encephalitis*:
        - **Etiology and pathogenesis**:
            - **Viral invasion of the brain producing lymphocytic inflammatory reaction with necrosis of neurons and glia**.
            - **The most common cause of encephalitis** → HSV-1
            - **Others include**: Herpes zoster, CMV, EPV, Adenoviruses, Mumps.
            - May occur in epidemics as a result of **Arbovirus infection** in parts of the world where mosquitos act as vectors for the disease.
        - **Clinical features**:
            - 1- Fever. 2- Headache. 3- Deteriorating level of consciousness over hours or days. 4- Seizures. 5- Focal signs. 6- Hemispheric signs (dysphasia, hemiparesis) increase the likelihood of HSV encephalitis.
        - **Investigations**:
            - 1- CT and MRI (exclude mass lesions and show brain swelling). 2- CSF (high pressure, lymphocytosis, high protein, normal glucose, viral antibody titers). 3- EEG (abnormal with evidence of diffuse brain dysfunction + characteristic periodic complexes over the temporal region).
            - **Early diagnosis → viral antigen immunoassay + PCR for amplification of viral DNA**.
        - **Management**:
            - **Acyclovir** (10mg/kg IV every 8 hours for 14 days) → should be started early without waiting for the results of detailed CSF studies and without brain biopsy, to prevent complications.

        - **Ganciclovir** → If CMV is suspected.
        - **Supportive measures**: 1- anti-epilepsy drugs (for seizure) 2- dexamethasone / mannitol (for worsening cerebral edema).
    - *Herpes Zoster*:
        - **Varicella zoster** which is dormant in dorsal root ganglia after an initial chickenpox infection may reactivate as shingles.
        - Localized pain + itching followed by Vesicular rash which affects single dermatome or adjacent dermatomes often on the trunk
        - After healing of rash → pain may persist (**post-herpetic neuralgia)**.
        - **Variants**:
            - **Zoster ophthalmicus**: rash involving the ophthalmic division of trigeminal nerve with risk of corneal damage and facial post-herpetic neuralgia.
            - **Ramsey Hunt syndrome**: unilateral LMN facial palsy and vesicles in the external auditory meatus + severe ear pain + vertigo + tinnitus + hearing loss.
            - **Motor zoster**: muscle weakness involving myotomes at a similar level to the dermatomes affected by rash.
        - **Treatment**: -usually self-limiting disease-
            - High doses of Acyclovir to speed healing and reduce pain and the risk of complication.
        - Zoster infection produce more severe manifestations especially in **immunocompromised** including generalized rash and encephalitis.
        - **Zoster myelitis**: involvement of the spinal cord presenting as hemiplegia.
    - *Retroviral infections*:
        - Infection with HIV may lead to neurological symptoms due to: 1- the virus itself has an affinity for neural tissue. 2- the risk of opportunistic infections and unusual neoplasms

involving the nervous system as a result of immunocompromise.

- **Cerebral toxoplasmosis**: focal hemispheric (hemiparesis, dysphasia, extrapyramidal disorders) cerebellar or cranial nerve deficits in an AIDS patient.
    - Presenting with Headaches + Seizures + CT or MRI evidence of focal or multifocal encephalitis (warranting **anti-toxoplasma treatment with Pyrimethamine, Folinic acid and either Sulphadiazine or Clindamycin**).
    - Brain biopsy to non-responders.
- **Cryptococcal meningitis**:
    - **The most common cause of meningitis in AIDS patients** is the yeast Cryptococcus neoformans.
    - Presents with 1- acute and subacute headache. 2- Fever. 3- seizures and focal deficits. 4- CSF (lymphocytosis, raised protein, low glucose).
    - Cryptococci may be identified on an **Indian ink preparation** or by **Detection of antigen in CSF or blood**.
    - **Treatment**: combined antifungal drugs (**Amphotericin B and Flucytosine**).
- **Herpesviruses**:
    - CMV is common in AIDS patients and may cause encephalitis or cord involvement.
- **Progressive multifocal leukoencephalopathy (PML)**:
    - Opportunistic infection by **Papovaviruses** resulting in multiple white matter lesions in the cerebral hemisphere, brainstem, and cerebellum.
    - Presents with progressive dementia and focal deficits.
    - PML may occur in other immunodeficiency states (hematological malignancy, TB, sarcoidosis).
- **Cerebral lymphoma**:

        - Focal or multifocal disease in cerebral hemispheres and posterior fossa (clinically and on CT and MR).
        - **Diagnosis** by brain biopsy in non-responders to anti-toxoplasma therapy.
    - All these complications are reduced by **Highly active antiretroviral therapy.**
- *Other viruses*:
    - **Poliomyelitis**:
        - Rare in developed countries after the development of immunization.
        - In epidemics, patients experienced minor illness characterized by: 1- headache. 2- fever. 3- vomiting 7-14 days after the virus entered the body through the gut or nasopharynx. 4- paralytic stage (as the virus gained access to the CNS) with meningitis, spinal and limb pain. 5- bulbar and respiratory failure.
        - Clinical features of LMN damage with variable patchy asymmetrical muscle involvement, fasciculations, wasting and areflexia.
        - Some recovery occurs at the end of the paralytic stage.
        - Many patients are left with permanent weakness, and few require long-term ventilatory support.
    - **Rabies**:
        - Acquired by the bite of an infected dog but may be transmitted by other mammals.
        - The virus migrates slowly to the CNS eliciting inflammatory reaction with diagnostic intracytoplasmic inclusions (**Negri bodies**).
        - Patients experience laryngospasm and terror on attempting to drink → **Hydrophobia**.
        - If the inflammation involves predominantly the spinal cord there is flaccid paralysis (dumb or paralytic rabies)

        - Prophylactic immunization is available for those handling potentially affected animals.
        - **Active and passive immunizations should be commenced immediately after the bite**.
    - **Postviral phenomena**:
        - **Subacute sclerosing panencephalitis**: late and fatal complication of measles infection.
        - **Acute disseminated encephalomyelitis**.
        - **Guillain-Barre' syndrome**: associated with antecedent infection, often viral.
        - **Postviral fatigue syndrome**: following EBV infections.
- **Other infections and transmissible disorders**:
    - *Protozoa*:
        - **Malaria**: should be considered and excluded on blood films of patients coming from endemic areas.
            - **Plasmodium Falciparum causes Hemorrhagic encephalitis**.
        - **Toxoplasmosis**: in addition to causing multifocal encephalitis in AIDS patients, it may also be acquired in utero causing Hydrocephalus, Intracranial calcifications, Choroidoretinitis.
        - **Trypanosomiasis**: presents as low-grade encephalitis with hypersomnolence and seizures.
    - *Metazoa*: encysted tapeworm larvae may present as cerebral lesions.
        - **Hydatid disease**: cysts act as intracranial masses, but rupture may result in chemical meningitis.
        - **Cysticercosis**: multiple cysts may lead to 1- epilepsy. 2- raised ICP. 3- focal signs. 4- hydrocephalus.
            - Treatment with Praziquantel + Steroids.

CHAPTER 16: MULTIPLE SCLEROSIS

- **Multiple sclerosis**: a disorder characterized by lesions separated both in space and time in the CNS, affecting mostly young people.
- **Pathology and Pathophysiology**:
  - Primarily affects the white matter in the brain and the spinal cord and the optic nerve.
  - There are relatively normal appearing regions of white matter interspersed with foci of inflammation and demyelination known as **Plaques** (located near venules).
  - **Inflammatory demyelination** of CNS tracts leads to reduction in their conduction velocity with distortion and ultimately loss of information conveyed along these pathways.
  - At early stages there is local breakdown of the BBB → evidence of inflammation with edema → loss of myelin and eventually the CNS equivalent of scar tissue (Gliosis).
  - The final result of shrunken area of sclerosis may be associated with little clinical deficit compared with that present when the plaque was pathologically most active because of Remyelination and return of normal function with resolution of edema and inflammation.
  - This clinical pattern is referred to as **MS relapses**, with symptoms being present being present for a period, then resolving partially or completely.
- **Etiology and pathogenesis**:
  - An environmental agent (e.g., a virus) triggers the condition in genetically susceptible individual.
  - Also, immune mechanisms play a role, evidenced by the presence of chronic inflammatory cells in active plaques and linkage of the condition to specific genes of MHC.
  - Familial disease, with higher concordance among monozygotic (identical) twins.
- **Epidemiology**:
  - More common in areas of temperate climate.

    - Individuals born in area of high risk will carry the risk if they migrate to an area of lower risk, but only if immigration occurs after the mid-teens.
    - More common in Females (3:1), may develop at any age, though its first onset is rare in children and elderly.
    - **Typical age of presentation 20 – 40 years**.
- **Clinical features**:
    - *Presentation*: 1- Visual disturbances. 2- Limb weakness. 3- Sensory disturbances.
        - **Visual disturbances**:
            - **Optic neuritis**:
                - A characteristic visual disturbance.
                - Inflammatory demyelination of one or less commonly both optic nerves.
                - *Symptoms include*: 1- pain around one eye (particularly with eye movement). 2- blurry vision (may proceed to complete monocular blindness within days or weeks). 3- loss of color vision.
                - *On examination*: 1- impaired visual acuity and color vision. 2- pink, swollen optic disk on fundoscopy. 3- visual field defects (typically a central scotoma). 4- relative afferent pupillary defect.
                - It resolves within a period of weeks to months, though some patients may be left with some impairment of vision, and fundoscopy will reveal optic disk pallor caused by optic atrophy.
                - Optic disk swelling in acute phase should be distinguished from papilledema caused by raised intracranial pressure (in the latter visual acuity is preserved and the only field defect in papilledema is enlargement of the physiological blind spot).

        - A single episode of optic neuritis doesn't signify that the patient will subsequently develop MS.
        - *Other visual disturbances*: 1- Diplopia (with vertigo and nausea → indicative of brainstem plaque).
    - **Sensorimotor disturbances**:
        - Imply that the lesion is in the spinal cord or cerebral hemispheres.
        - *The patient may present with*: 1- asymmetrical spastic paresis and or paraesthesia. 2- thermal anesthesia. 3- dysesthesia in the limbs.
        - A lesion in the posterior column may produce rapid tingling sensation shooting down the arms or legs on neck flexion (**Lhermitte phenomenon**).
        - **Uhthoff phenomenon**: motor, sensory or indeed visual symptoms are temporarily much worse after a hot bath.
    - *Other presentations*: 1- Pain is less common in MS, though some patients may experience typical trigeminal neuralgia as a result of brainstem plaque. 2- some patients may present with bladder disturbance (urgency of micturition or urinary retention) and impotence.
- **Course**:
    - Clinical features worsen over days or weeks, reaching a plateau and then gradually resolve partially or completely.
    - There may be recurrences at unpredictable intervals, affecting the same or different parts of the CNS.
    - With initial episodes there may be complete or near-complete symptomatic resolution → **relapsing-remitting disease**.
    - Subsequent episodes of demyelination may leave some residual disability, the patient eventually entering a secondary phase of steady progression without resolution → **secondary progressive disease**.

- Some patients (presenting in middle-life with spastic paraparesis) will have no clear-cut relapses and remissions → **primary progressive disease.**
- Occasionally, the disease is hyperacute with death occurring within months, but the average life expectancy in patients with progressive disease exceeds 25 years from onset.
- Long-term prognosis is generally poor.

- **Diagnosis**:
  - Clinical diagnosis based on the occurrence of at least 2 lesions in the CNS separated in time and space.
  - *Salient investigations*:
    - **MRI of the brain and spinal cord** → reveal lesions corresponding to plaques, however those aren't specific for MS and some patients may have false-negative MR scans.
      - Criteria have now been developed whereby its possible to diagnose MS after a first clinical attack (clinically isolated syndrome) on the basis of strictly defined MR features.
    - **Visual evoked potentials (VEPs)** → show delayed central conduction in the visual pathways (as a result of previous optic neuritis).
    - **CSF examination** → 1- Lymphocytosis. 2- Raised protein (particularly immunoglobulins). 3- Detection of Oligoclonal bands by electrophoresis, indicating local synthesis of immunoglobulins within the CNS.
  - These tests are neither 100% specific nor sensitive to MS.
  - Even if symptoms seem likely to be due to MS, investigation isn't necessarily indicated in the absence of limitation of function.
  - Investigations are more important in patients with primary progressive disease where the classical diagnostic criteria are not applicable.
    - These patients present with a progressive spastic paraparesis so the salient investigation in their case is spinal imaging by MR to exclude a compressive lesion of the spinal

cord (tumor) which is the main DDx and is potentially treatable.

- *Other DDx*:
  - **For relapsing and remitting disease**: 1- Sarcoidosis. 2- SLE. 3- TIA.
  - **For progressive disease**: 1- Motor neuron disease. 2- Spinal and cerebellar degeneration.

- **Management**:
  - *Management of Acute relapses*:
    - **First line**: Corticosteroids; given in the form of high-dose *Methylprednisolone* IV or Orally (500mg to 1g daily for 3-5 days).
    - Improve the speed but not the degree of recovery from exacerbations.
    - Exclude UTI before starting a course of corticosteroids.
  - *Modification of the course of the disease*:
    - **Immunosuppressant drugs** (e.g., Azathioprine, MTX, Cyclophosphamide).
    - Any marginal benefits from these agents are outweighed by their side effects.
    - **More novel immunotherapeutic agents** with the aim of altering the rate of progression of MS or at least reducing relapse rate (e.g., Interferon beta, Glatiramer acetate).
    - **A monoclonal antibody** (natalizumab) is approximately twice as effective as interferon beta and is used treat aggressive relapsing remitting MS (carries a low risk of progressive multifocal leukoencephalopathy).
    - **Mitoxantrone** (a chemotherapeutic agent), an alternative to natalizumab, but also has potentially serious adverse effects including cardiotoxicity and a risk of acute leukemia.
  - *Control of symptoms*:
    - **Spasticity, flexor spasms** → Baclofen (oral or intrathecal), Dantrolene, Tizanidine, Diazepam; though these drugs may *increase weakness and cause drowsiness*. Other options include injection of botulinum toxin in the affected muscles.

        - **Cerebellar tremor** → if mild it may respond to Clonazepam, Isoniazid, Gabapentin.
        - **Fatigue** → Amantadine, Selegiline, Modafinil (anti-narcolepsy medication).
        - **Bladder disturbances** → Anti-cholinergic drugs (*Oxybutynin* / *Tolterodine*).
        - **Depression** → Tricyclic and related drugs in low dosages (*Amitriptyline* / *Dosulepin*); Selective serotonin reuptake inhibitors (*Sertraline*).
        - **Erectile impotence** → Phosphodiesterase type 5 inhibitor (*Sildenafil*), Intracavernosal Papaverine or Prostaglandins (given also by urethral application).
        - **Pain and paroxysmal symptoms including seizures** → Carbamazepine, Gabapentin.
        - Worsening urinary difficulty may necessitate urethral or suprapubic catheterization.
        - **Other surgical measures**: 1- Tenotomy for spasticity and flexor spasms. 2- Dorsal column stimulation for pain. 3- Stereotactic thalamotomy for severe cerebellar ataxia.
- **Other diseases of myelin**:
    - **Inherited disorders**:
        - Genetic disorders of myelin chemistry lead to abnormal myelin formation (Dysmyelination) → **Leukodystrophies**.
        - Usually, present in infancy or childhood, however some develop in adulthood with dementia, ataxia, spasticity, seizures, optic atrophy, and sometimes peripheral nervous system involvement.
        - **No specific treatment**, but there is an interest in enzyme replacement by bone marrow transplantation or ultimately gene therapy.
    - **Acquired diseases**:
        - **Acute disseminated encephalomyelitis**:
            - A rare disease, characterized by acute multifocal inflammatory demyelination throughout the CNS, it

may follow viral infection or immunization, AKA **postinfectious encephalomyelitis**.
    - *Patients present with*: 1- Fever. 2- Headache. 3- Meningism. 4- Impairment of consciousness. 5- Focal signs and symptoms.
    - *Investigations*: 1- CSF (lymphocytosis + raised protein). 2- EEG (non-specific changes). 3- Imaging by CT may be normal. 4- MR (appearance similar to MS).
    - *Treatment*: Corticosteroids (high-dose IV methylprednisolone).
    - The long-term prognosis is good with complete recovery and no prolapse.
- **Neuromyelitis Optica (Devic's disease)**:
    - Characterized by **optic neuritis** (unilateral or more typically bilateral) and **transverse myelitis**.
- **Central pontine myelinolysis**:
    - Associated with alcoholism and with hyponatremia.
    - Presents acutely with features of pontine and medullary lesions; bulbar palsy, tetraparesis, eye movement disorders, coma.
    - *Treatment*: 1- Gradual correction of metabolic abnormalities. 2- Vitamin supplements.
    - Poor prognosis.

CHAPTER 17: NERVE AND MUSCLE

- **Peripheral nerve disorders**:
  - *Definitions*:
    - **Mononeuropathy**: peripheral nerves damaged individually by trauma, particularly pressure (as with DM), or by damage to their blood supply - the vasa nervorum – (as with vasculitis) → may lead to multifocal neuropathy (*mononeuritis multiplex*).
    - **Polyneuropathy**: multiple peripheral nerves are commonly affected by inflammatory, metabolic, or toxic processes that lead to diffuse, distal symmetrical pattern of damage usually affecting the lower limbs before the upper limbs.
  - **Mononeuropathies**:
    - **Carpal tunnel syndrome**:
      - Compression of the median nerve at the wrist as it passes through the carpal tunnel.
      - Could be isolated in patients with manual occupation, or in disorders that renders the nerve sensitive to pressure as with DM, or when the carpal tunnel is crowded with excessive or abnormal soft tissue.
      - **Clinical features**: 1- pain in the hand or arm (especially at night or at exertion). 2- wasting and weakness of the muscles of the thenar eminence. 3- sensory loss in the hand (in the distribution of the median nerve). 4- tingling paraesthesia in the distribution of the median nerve following percussion of the palm in the region of the carpal tunnel (**Tinel's sign**) or maximum passive flexion of the wrist for 60 seconds (**Phalen's test**). 5- Bilateral involvement.
      - **Diagnosis**: Hx and Px and confirmed electrodiagnostically or by ultrasound of the wrist.
      - **Investigations**: 1- Blood glucose. 2- ESR. 3- Thyroid function.

- **Treatment**: 1- Splinting the hand (especially at night) in a position of partial wrist extension. 2- Local injection of the carpal tunnel with corticosteroids. 3- surgical decompression of the median nerve at the wrist

Table 17.1 General medical associations of carpal tunnel syndrome.

Pregnancy
Diabetes mellitus
Local deformity, e.g. secondary to osteoarthritis, fracture
Rheumatoid arthritis
Myxoedema
Acromegaly
Amyloidosis

- **Ulnar neuropathy**:
  - The ulnar nerve is subjected to damage from pressure anywhere along its course but particularly at the elbow.
  - **Clinical features**: 1- Pain and/or tingling paraesthesia radiating from the elbow down the forearm to the ulnar border of the hand. 2- Wasting and weakness of the intrinsic muscles of the hand (sparing the thenar eminence). 3- sensory loss in the hand in the distribution of the ulnar nerve. 4- characteristic Claw hand deformity in chronic lesions.
  - **Diagnosis**: Nerve conduction study (NCS).
  - **Treatment**: 1- mild lesions respond to splinting the arm at night, with the elbow extended to reduce the pressure on the nerve. 2- for more severe lesions, surgical decompression, or ulnar nerve transposition.

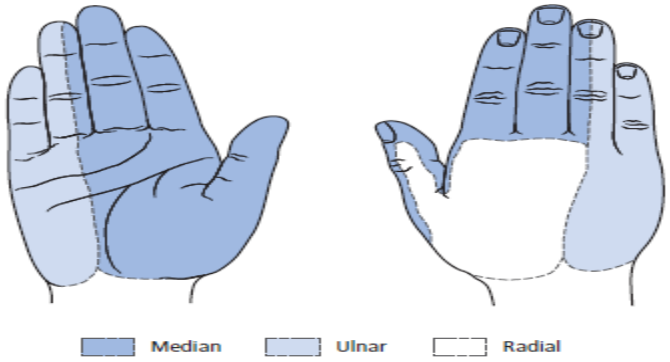


Figure 17.1 Cutaneous distributions of the median, ulnar and radial nerves.

- **Radial palsy**:
  - Pressure on the radial nerve in the upper arm may lead to an acute Wrist drop and sometimes sensory loss in the distribution of the superficial radial nerve.
  - Occurs as a consequence of prolonged period of abnormal posture of the upper arm (**Saturday night palsy**: the upper arm is draped awkwardly over an armchair because of alcohol intoxication).
- **Brachial plexus lesions**:
  - Caused by an acute trauma to the brachial plexus (Road accidents usually involving motorcyclists – upper roots of plexus (**Erb's paralysis**) or lower roots (**Klumpke's paralysis**)-)
  - **Cervical rib**:
    - May compress the brachial plexus at the thoracic outlet.
    - **Diagnosis**: 1- surgical exploration of the brachial plexus (for patients with progressive wasting and weakness of the intrinsic hand muscles, appropriate sensory loss, and support from electrodiagnostic studies). 2- radiographs (reveal a cervical rib, but compression may

result from a fibrous band invisible on plain x-ray).

- **Pancoast tumor**:
  - Bronchogenic carcinoma at the lung apex may invade the lower roots of the brachial plexus.
  - **Clinical features**: 1- progressive pain in the ipsilateral arm. 2- distal wasting and weakness. 3- sensory loss (C7, C8, T1 dermatomes). 4- Horner's syndrome (involvement of the pre-ganglionic sympathetic fibers).
  - Diagnostic difficulties may arise with breast carcinoma with previous local radiotherapy → involvement of the plexus may be due to invasion by tumor or radiation plexopathy.
- **Acute branchial neuritis (AKA Neuralgic amyotrophy or Idiopathic brachial plexopathy)**:
  - Characterized by severe pain in the shoulder and arm at onset.
  - No obvious cause, but it may follow immunization or operation.
  - When the pain subsides → patchy wasting and weakness of periscapular and more distal upper limb muscles.
  - Serratus anterior muscle group may be involved resulting in Winging of the scapula.
  - More often unilateral.
  - Electrodiagnostic studies are unhelpful, CSF is normal.
  - No specific treatment, spontaneous recovery of function within 18 months – 2 years.

▪ **Meralgia paraesthetica**:

- Compression of the lateral cutaneous nerve of the thigh as it passes under the inguinal ligament produces characteristic sensory loss.

        - The onset is associated with a change in the patient's weight.
    - **Lateral popliteal palsy**:
        - Damage to the common peroneal nerve as it winds around the fibular neck leading to foot drop.
        - There is weakness of the ankle dorsiflexion and eversion and of the extensor hallucis longus with variable sensory loss.
        - Occurs commonly in immobile patients and those whose nerves are prone to damage from pressure as with DM, may also result from a lumbar root lesion (L5 usually).
        - Damage to the peroneal nerve is often reversible being caused by conduction block (neurapraxia).
        - Patients benefit from a foot drop splint.
- **Multifocal neuropathy**:
    - **Causes**: 1- Malignant infiltration (carcinoma or lymphoma). 2- Vasculitis or connective tissue disease (RA, SLE, Polyarteritis nodosa, Wegener's granulomatosis). 3- Sarcoidosis. 4- DM. 5- Infection (Leprosy, HZV, HIV, Lyme disease). 6- Hereditary neuropathy with liability to pressure palsies.
    - *Multifocal neuropathies due to vasculitis* presents with pain, weakness, and sensory loss in the distribution of multiple peripheral nerves.
    - *The lower limbs are more commonly affected*.
- **Polyneuropathy**:
    - May be subclassified according to whether there is sensory or motor involvement or both.
    - Further subdivision pathophysiologically, depending on whether the site of the disease is the myelin sheath or the nerve fiber itself (**demyelinating and axonal neuropathies** respectively).

Table 17.2 Causes of polyneuropathy.

Inherited
See Chapter 18
Infection
Leprosy
Diphtheria
Lyme disease
HIV
Inflammatory
Guillain–Barré syndrome (Chapter 20)
Chronic inflammatory demyelinating polyneuropathy
Sarcoid
Sjögren's syndrome
Vasculitis – lupus, polyarteritis
Neoplastic
Paraneoplastic (Chapter 19)
Paraproteinaemic
Metabolic
Diabetes mellitus
Uraemia
Myxoedema
Amyloid
Nutritional
Vitamin deficiency, especially thiamine, niacin and B_{12}
Toxic
For example, alcohol, lead, arsenic, gold, mercury, thallium, insecticides, hexane
Drugs
For example, isoniazid, vincristine, cisplatinum, metronidazole, nitrofurantoin, phenytoin, amiodarone

- **Presentation**: 1- distal numbness and/or paraesthesia or pain. 2- motor symptoms (distal weakness and wasting). 3- foot and hand deformity in longstanding neuropathy (Pes cavus and Claw hand). 4- severe sensory loss leading neuropathic ulceration and joint deformity. 5- coexistent symptoms.
- **Clinical signs**: 1- signs of distal LMN involvement and muscle wasting, weakness, and tendon areflexia. 2- distal position sense loss may result in sensory ataxia. 3- characteristic glove-and-stocking distribution of impairment of pain, temperature, and touch sensation. 4- peripheral nerves may be thickened.
- **Treatment**: - depends on the cause-
    - Acute inflammatory demyelinating polyneuropathy (**Guillain-Barre' syndrome**) is potentially a neurological emergency.
    - Chronic inflammatory demyelinating polyneuropathy (CIDP) and Vasculitic neuropathies may require corticosteroid therapy and/or immunomodulatory

measures including immunosuppressants (*Azathioprine*, *Cyclophosphamide*, *Cyclosporin*), IVIg, or plasma exchange.

- It's important to distinguish Guillain-Barre' syndrome and CIDP (diseases of the peripheral nervous system) from Demyelination of the CNS.

Table 17.3 Investigation of polyneuropathy.

Blood tests Full blood count, sedimentation rate, glucose, urea, electrolytes, liver and thyroid function, vitamin B_{12}, serum protein electrophoresis, auto-antibodies
Urine Microscopy for evidence of vasculitis, glucose, porphyrins, Bence Jones protein
CSF Raised protein, particularly in inflammatory neuropathies
Neurophysiology Nerve conduction studies and EMG
Chest X-ray For sarcoidosis, carcinoma
Special investigations for selected patients Nerve biopsy, when the cause of a deteriorating neuropathy is unknown despite extensive investigation, also to confirm vasculitis, leprosy and chronic inflammatory demyelinating polyneuropathy Bone marrow biopsy, skeletal survey for suspected myeloma Specific blood tests for particular suspected conditions, e.g. DNA analysis for hereditary neuropathies, white cell enzymes for inborn errors of metabolism, *Borrelia* antibodies for Lyme disease

Table 17.4 Diseases causing demyelination, classified according to site and time course.

	Central nervous system	Peripheral nervous system
Acute	Acute disseminated encephalomyelitis (ADEM) (Chapter 16) – rare	Guillain–Barré syndrome (Chapter 20) – relatively common
Chronic	Multiple sclerosis (Chapter 16) – common	Chronic inflammatory demyelinating polyneuropathy (CIDP) – rare

- **Neuromuscular junction**:
  - **Myasthenia gravis**:
    - Autoimmune disorder in which most patients have circulating antibodies to acetylcholine receptors at the neuromuscular junction.

- There may be associated **thymus pathology** (hyperplasia, atrophy of the tumor – thymoma).
- Rare disease, all age groups may be affected.
- **Clinical features**:
    - 1- Fatigable ptosis. 2- Diplopia with limitation of eye movement. 3- Facial weakness (myasthenic snarl, weakness of eye closure). 4- Bulbar signs and symptoms (dysphagia with nasal regurgitation of liquids, dysarthria). 5- Involvement of respiratory muscles. 6- Neck and limb muscle weakness, worse at the end of the day and after exercise (fatigability).
- **Investigations**: 1- Serum acetylcholine receptor antibody analysis (15% of patients are negative but have other autoantibodies). 2- Tensilon test (transient and rapid improvement in clinical features after IV injection of Edrophonium); test best performed 'double-blind' with atropine and cardiac resuscitation equipment available for muscarinic effects of excess acetylcholine. 3- EMG. 4- Thyroid function test (for associated thyrotoxicosis). 5- Striated muscle antibody analysis (positive in patients with thymoma). 6- CT scan of the anterior mediastinum (for thymic enlargement).
- **Treatment**:
    - **Anticholinesterase (Pyridostigmine**), provide symptomatic relief. Patients requiring increasing doses may develop muscarinic cholinergic side effects; increased salivation, vomiting, abdominal pain, diarrhea.
    - **Corticosteroids (Prednisolone)**, for moderately severe disease not responding to other treatment. Should be gradually increased from a low dosage as symptoms may initially worsen.
    - **Immunosuppression (Azathioprine**), in combination with corticosteroids for moderately severe disease.

        - **Thymectomy**, for thymoma and for younger patients early in the course of the disease to reduce requirements for medical therapy and achieve complete remission.
        - **Plasma exchange or IV immunoglobulin** in preparation for thymectomy and in severe disease.
        - Avoid certain antibiotics such as Aminoglycosides; because of their blocking effect at the neuromuscular junction.
    - **Other myasthenic syndromes**:
        - The neuromuscular junction may rarely be the site of congenital disease or of paraneoplastic disorder (**Lambert-Eaton myasthenic syndrome**).
- **Myopathy**:
    - **Clinical features**: 1- Weakness of the trunk and proximal limb muscles. 2- Dysphagia. 3- Weakness of neck flexion and/or extension and of muscles of facial expression. 4- Waddling gait.
    - In acquired disorders muscle wasting may be relatively mild at least in early stages and the tendon reflexes spared.
    - **Investigations**: 1- Blood tests (*ESR*, *Autoantibodies*, *CK*). 2- EMG. 3- Muscle biopsy.

Table 17.5 Causes of primary muscle disease.

Inherited
Muscular dystrophies
Metabolic myopathies
Infection
Gas gangrene
Staphylococcal myositis
Viral infection – especially influenza, Coxsackie, echo
Parasites – cysticercosis, trichinosis
Inflammation
Polymyositis
Dermatomyositis
Sarcoid
Neoplastic
Dermatomyositis – may be a paraneoplastic phenomenon (Chapter 19)
Metabolic (acquired)
Thyrotoxicosis
Cushing's syndrome
Osteomalacia
Toxic/drug induced
Corticosteroids
Halothane – 'malignant hyperpyrexia' (rare)
Other drugs may rarely be associated with myopathy
Degenerative
Inclusion body myositis

- **Specific disorders**:
    - **Muscular dystrophies**:
        - **Dystrophinopathies**:
            - Caused by mutations of the X-linked gene for the muscle protein dystrophin.
            - The childhood form (**Duchenne muscular dystrophy**) is severe.
                - Affected boys develop proximal muscle weakness in early childhood + difficulty raising from squatting position, using their hands to climb up their legs (**Gower's sign**) + pseudohypertrophy of calf muscles because of replacement of muscle fibers by fatty connective tissue.
                - Children are usually confined to a wheelchair before their teens.
                - Death usually from cardiac and respiratory complications before the age of 20.
            - Less severe mutations in adolescence or adult life (**Becker muscular dystrophy**) and be compatible with normal lifespan.
            - Distinction from other limb-girdle dystrophies is possible through molecular analysis of the dystrophin gene.
    - **Other muscular dystrophies**:
        - **Myotonic dystrophy**: autosomal dominant disorder in which patients characteristically have abnormally sustained muscle contraction or myotonia.
            - Manifest as inability to release the grip.
            - Striking the muscle with patellar hammer may elicit percussion myotonia and the condition may also be diagnosed with electromyography.
            - **Other features**: 1- Bilateral ptosis. 2- Facial weakness. 3- Wasting and weakness of the

sternomastoid. 4- Cataracts. 5- Endocrine associations (DM, Frontal balding, Testicular atrophy).
        - **Treatment**: Phenytoin / Mexiletine
    - **Facioscapulohumeral muscular dystrophy**: autosomal dominant condition.
        - **Presentation**: 1- bilateral facial weakness. 2- winging of both scapulae. 3- weakness and wasting of proximal upper limb muscles. 4- weakness of the spinal and pelvic muscles. 5- waddling gait. 6- lumbar lordosis.
        - *Rarely affect the extraocular and pharyngeal muscles*.
- **Other inherited disorders**:
    - Metabolic defects such as glycogen storage disease may produce muscle weakness often with pain and cramps.
    - **Familial periodic paralysis**: bouts of profound muscle weakness, sometimes provoked by exercise, a high carbohydrate meal, or exposure to cold. May be associated with hypo/hyperkalemia.
- **Acquired disorders**:
    - **Inflammatory myopathies**:
        - **Polymyositis**: either isolated or in association with autoimmune connective tissue disorders (SS, Fibrosing alveolitis, Sjogren's syndrome).
        - **Dermatomyositis**: Inflammatory myopathy with a characteristic heliotrope rash affecting the face.
            - A purple-red rash may also involve the knuckles, anterior chest wall and other sites, particularly the extensor surfaces.
            - In minority of patients with dermatomyositis (males >45 y/o) there is underlying malignancy (carcinoma of the bronchus or stomach).
        - **Clinical features**: 1- same as proximal myopathies. 2- dysphagia (as a result of pharyngeal muscle

involvement). 3- muscle pain and tenderness. 4- arthralgia and Raynaud's phenomena.

- **Treatment**: Corticosteroids and Immunosuppressant drugs (Azathioprine).
- **Inclusion body myositis** → unresponsive to treatment.
    - Common cause of acquired muscle disease.
    - Affects elderly with characteristic selective involvement of the finger flexors and quadriceps muscles.

CHAPTER 18: DEVELOPMENT AND DEGENERATION

- **Charcot-Marie-Tooth disease (CMT)**:
  - AKA **Hereditary motor and sensory neuropathy**.
  - The most common variant (CMT1A) has an autosomal dominant pattern of inheritance and can be diagnosed by DNA analysis.
  - **Presentation**: 1- slowly progressive distal wasting and weakness (anterolateral muscle compartment of the leg). 2- pes cavus. 3- absent tendon reflexes. 4- mild sensory loss. 5- thickened peripheral nerves. 6- marked slowing of nerve conduction velocities.
  - CMT2 resembles type 1 but the age of onset may be later and nerve conduction velocity is relatively preserved, reflecting underlying axonal rather than demyelinating pathology.
  - *Prognosis is variable*, some patients are wheelchair-bound by the time they reach middle age, whereas others are asymptomatic throughout the normal lifespan.
- **Dementia**:
  - Significant impairment of 2 or more domains of cognition, one of which must be memory.
  - There must be no evidence of delirium.
  - **Alzheimer's disease**:
    - The most common cause of dementia in all age groups, with markedly increased frequency with elderly.
    - Characterized pathologically by Intracellular neurofibrillary tangles composed of paired helical filaments and extracellular neuritic plaques containing an amyloid core.
    - **Etiology and pathogenesis**:
      - The core of the neuritic plaques is composed of a peptide (Amyloid beta-protein), which is a fragment of much larger protein (Amyloid precursor protein), encoded by a gene on chromosome 21.

- Patients with **Down syndrome** develop premature features of AD and may be at risk of excess amyloid formation from their extra copy of the APP gene.
- A specific isoform of the lipid transport protein (Apolipoprotein E) has been identified as an independent risk factor for the development of both familial and sporadic AD.
- The end result of the pathogenetic process in AD is the death of neurons in specific areas of the cerebral cortex concerned with aspects of cognition (**the hippocampus and adjacent structures + the temporal neocortex + the nucleus basalis of Meynert in frontal lobe**).
- Cholinergic neurons are particularly affected → *you can use cholinergic-enhancing drugs to improve memory in this disease*.

- **Clinical features**: 1- memory loss (early in the course of the disease). 2- difficulty learning and retaining new information. 3- disorientation in time (as a result of impairment of memory and attention defects). 4- word-finding difficulties and loss of general knowledge. 5- hallucinations and delusions. 6- severe global loss of cognitive function (amnesia, dysphasia, dyspraxia, agnosia). 7- personality disintegrates with behavioral disturbances. 8- incontinence. 9- increasing dependance. 10- death within 5-10 years.
- **Diagnosis**:
  - There is **no specific test for AD**, application of clinical diagnostic criteria, and excluding other causes of dementia particularly those that are treatable.

Table 18.4 Causes of dementia.

Inherited
Familial Alzheimer's disease
Huntington's disease
Some cerebellar ataxias
Wilson's disease
Trauma
Subdural haematoma
Other severe head injuries
Infection
Syphilis
Subacute sclerosing panencephalitis
AIDS-related dementia
Progressive multifocal leucoencephalopathy
Cerebral Whipple's disease (associated with arthritis and gut symptoms)
Inflammation
Multiple sclerosis
Sarcoid, lupus, vasculitis
Neoplasm
Frontal tumours
Multiple cerebral metastases
Hydrocephalus secondary to posterior fossa tumour (**NB:** normal-pressure hydrocephalus, in the absence of a structural cause, may present with dementia – see text)
Paraneoplastic
Vascular
Multi-infarct dementia
Metabolic
Myxoedema
Vitamin B_{12} deficiency
Chronic organ failure – Chapter 19
Drugs/toxins
For example, barbiturates, alcohol, lead
Degenerative
Alzheimer's disease
Dementia with Lewy bodies
Frontotemporal dementia
Prion diseases – may also be considered both inherited and transmissible
Parkinson's disease and other akinetic–rigid syndromes (see text)

- **Management**:
  - Systemic illness such as infection can exacerbate dementia → *attention to the patient's general health including avoidance of sedatives, alcohol, and fatigue*.
  - *Simple memory aids*.
  - *Patients should wear MedicAlert bracelets*.
  - *Various cholinergic-enhancing drugs → improve memory early in the disease (for only few months*).
    - **Donepezil**, **Rivastigmine**, **Galantamine**.
  - *Symptomatic treatment with donepezil*.
  - *Antidepressants, Neuroleptics, Anxiolytics*.

- **Other causes of dementia**:

- **Degenerative diseases**:
  - **Prion disease**: a group of rare neurodegenerative disorders in animals and man.
    - Histological characteristic → *Spongiform encephalopathies*.
    - **Creutzfeldt-Jakob disease**, a human disorder, both inherited and transmissible.
    - The molecular basis of these phenomena resides in the infectious pathogen of the spongiform encephalopathies termed **Prion** (composed entirely of protein – prion protein- with no evidence of nucleic acid component and is highly resistant to heat and formaldehyde).
    - *Most cases of CJD are sporadic* → by somatic mutation of the PrP gene.
    - **Familial CJD** is inherited as autosomal dominant trait and is due to point mutation of PrP gene.
    - **Infectious CJD** → 1- following accidental inoculation of patients with prions at surgery. 2- corneal graft. 3- the use of GH made from human pituitary extracts.
    - **Clinical features**: 1- rapidly progressive dementia. 2- death within 1-2 years or less. 3- cortical visual problems and motor features (myoclonus, muscle wasting, fasciculations).
    - **Variant CJD** occurs in younger patients and present with psychiatric features, sensory disturbance, and ataxia before the onset of dementia.
    - **Diagnosis**: 1- EEG (periodic complexes). 2- MR (characteristic appearance of the thalamus). 3- CSF (high level of neuronal protein). 4- Biopsy

or Autopsy – brain or lymphoid tissue; tonsils- (to confirm diagnosis).
    - **Treatment**: no proven treatment.
- **Frontotemporal dementia**: neurodegeneration confined to the frontal and temporal lobes.
    - Patients present with dementia of frontal type; changes in personality, behavior and other executive functions often associated with progressive non-fluent dysphasia (focal frontal lobe atrophy).
    - Presents in younger patients.
- **Semantic dementia**: word-finding difficulties and loss of general knowledge (focal temporal lobe atrophy).
    - Progressive fluent dysphasia.
- **Dementia with movement disorders**, e.g., Huntington's disease and Progressive supranuclear palsy.
    - The dementia is often described as subcortical with prominent slowing of cognitive function (bradyphrenia), personality and mood changes and relative absence of focal cortical deficits typical of AD.
- **Dementia with Lewy bodies (DLB)**: shows a mixture of cortical and subcortical features.
    - Recognized as a relatively common neurodegenerative cause of dementia, second only to AD.
    - *Lewy bodies are the major histological features of Parkinson's disease when confined to nigrostriatal neurons*.
    - In the case of dementia, **Lewy bodies are more widely distributed**.
    - **Distinguishing features of DLB**: 1- fluctuating cognition with nocturnal confusion. 2- visual hallucinations. 3- evidence of parkinsonism. 4-

worsening clinical features with neuroleptic and antiparkinsonian drugs, even in small doses.

- Patients with idiopathic Parkinson's disease commonly develop dementia some years after the onset of the movement disorder (**Parkinson's disease with dementia -PDD**-).
  - In such circumstances it's difficult to know whether the patient has AD superimposed on Parkinson's disease or has developed more widespread Lewy body changes.
- *Patients are said to have DLB if the movement disorder and dementia present within a year of each other, and PDD if the onset of dementia is delayed by more than a year after the emergence of parkinsonism.*

- **Non-degenerative causes of dementia**:
  - **Vascular (multi-infarct) dementia**:
    - Common condition, caused by recurrent thromboembolism from extracranial sources, more commonly small vessel disease in the brain.
    - **Clinical features**: 1- abrupt onset of stepwise progression, unlike the typical gradual progression of AD. 2- presence of vascular disease elsewhere and of vascular risk factors. 3- combined cortical and subcortical deficits. 4- nocturnal confusion, fluctuating cognition. 5- emotional lability and other features of pseudobulbar palsy.
    - **Treatment**: management of vascular risk factors to avoid further progression.
  - **Chronic subdural hematoma**:

    - Occurs predominantly in the elderly and may follow relative minor head injury.
    - **Typical presentation**: elderly predisposed to hematoma formation by cerebral atrophy and stretching of subdural veins, minor head trauma may trigger bleeding.
    - A gradually expanding cavity develops, filled with yellow or brown fluid as a result of breakdown of blood and surrounded by a membrane.
    - Expanding hematoma exerts mass effect with shift of midline structures (unless bilateral hematoma).
    - Patients may solely present with dementia but also there may be fluctuations in conscious level, epilepsy, signs of raised ICP and focal neurological deficits.
    - **Investigation**: CT scan (difficulties may arise early in the course of the condition when the hematoma is isodense with brain tissue, particularly if bilateral hematomas and hence no midline shifting).
    - **Treatment**: surgical evacuation of the hematoma through burr holes often with dramatic benefit.
- **Normal pressure hydrocephalus**:
    - **Triad** of: 1- dementia. 2- gait disturbance. 3- early urinary incontinence.
    - **Investigations**: 1- CT (Gross ventricular enlargement without cortical atrophy). 2- Lumbar puncture (normal CSF pressure).
    - *Continuous ICP monitoring over 1-2 days may reveal waves of raised pressure*.
    - **Treatment**: surgical treatment by ventriculoperitoneal shunt.

- **Motor neuron disease**:
  - AKA **Amyotrophic lateral sclerosis** (ALS): progressive degenerative disorder of cortical, brainstem, and spinal motor neurons.
  - **Epidemiology**:
    - Slight male predominance.
    - More common in middle-aged and elderly (peak onset ~60 years).
    - 5-10% positive family Hx (autosomal dominant).
    - Younger age of onset in hereditary cases.
    - In familial cases → mutation in the gene for the enzyme Superoxide dismutase.
  - **Etiology and Pathogenesis**:
    - **Excitotoxicity** → toxins interacting with glutamate receptors, resulting in cellular calcium overload.
    - **Free radicals** → motor neuron damage by a cascade of reactions initiated by electron capture by oxygen free radicals (superoxide and peroxide).
    - These 2 mechanisms may work together, so that oxygen free radicals are generated in response to calcium overload.
  - **Clinical features and prognosis**:
    - 1- wasting and weakness of upper limb muscles. 2- cramps and fasciculations. 3- dysarthria and dysphagia. 4- signs of mixed bulbar or pseudobulbar palsies (wasted, fasciculating tongue, but brisk jaw reflexes). 5- Chest infection (aspiration with ventilatory muscle weakness).
    - Difficulties in diagnosis arise when only LMN or UMN signs are present in one limb.
    - *Motor signs are asymmetrical initially*.
    - *Sensory signs are absent, and there is no sphincter involvement beyond constipation caused by pelvic and abdominal muscle weakness and reduced fluid intake.*
    - *Few patients develop dementia of frontal type*.
    - **Features of advanced disease**: 1- Depression. 2- Weight loss, malnutrition, and dehydration. 3- VTE. 4- Ventilatory failure (the usual cause of death).

- **Investigations and diagnosis**:
  - 1- EMG (widespread evidence of denervation as a result of anterior horn cells damage). 2- NCS (exclude other motor diseases with pure LMN features). 3- Spinal imaging by MR (exclude cord or root compression). 4- Exclusion of MG.
- **Management**:
  - **Drug treatment**:
    - 1- Anticholinergics (reducing saliva secretion when swallowing is difficult; other options include injection of botulinum toxin into the salivary glands). 2- Baclofen, Dantrolene, Tizanidine, Diazepam (for spasticity). 3- Quinine (for cramps). 4- Antidepressants. 5- Laxatives with increased fluid (for constipation). 6- Opiates, Diazepam (for symptomatic relief of dyspnea). 7- Riluzole (prolongs survival, but only for few months in selected patients).
  - **Other measures**:
    - 1- Physiotherapy. 2- Communication aids for dysarthria. 3- Adaptations at home. 4- Advice from speech therapists and dietitians for dysphagia. 5- Gastrostomy for more severe dysphagia. 6- Assisted ventilation for respiratory failure.