Chapter—2 (D) Pharmacotherapeutics Central Nervous System

(d) Central Nervous System

- Epilepsy
- Parkinson's disease
- Alzheimer's disease
- Stroke
- Migraine

Central Nervous System

Introduction—The principal functional unit of the central nervous system (CNS) is the neuron.

- Neuron is the structural and functional unit of the nervous system; it has the unique ability to receive and transmit information.
- Neurons of different types and in different locations have distinct properties, including functional roles, distribution of their connections, neurotransmitters used, metabolic requirements, and levels of electrical activity at a given moment.
- In addition to neurons the CNS contains other cells, such as astrocytes and oligodendrocytes, which make up the neuroglia. During any injury or abnormality these cells undergo a range of functional and morphological changes and leads to many of neurological disorders.

Clinical consideration—

- Epilepsy.
- Parkinson's disease.
- Alzheimer's disease.
- Stroke.
- Migraine.
- Encephalopathy
- Seizure.

- Meningoencephalitis.
- Cerebral palsy.

Epilepsy

Definition— Epilepsy is a neurological disorder in which brain activity becomes abnormal, causing seizures, sensations and sometimes loss of awareness.

- Epilepsy can cause by brain injury from stroke, trauma, a mass lesion, or infection. About two-thirds of new cases arise in children, and most of these cases are idiopathic or caused by trauma. In contrast, seizures or epilepsy with onset in adult life is more often due to underlying brain lesions or metabolic causes.

Classification of seizures— Seizure is classified on the basis of behavioural and electrophysiologic pattern of activity as-

1. **Partial (Focal seizures) —** It mainly appears in only one hemisphere. That means symptoms only happen in a specific part or on one side of your body. But focal seizures can sometimes spread and become generalized seizures.
    a. Simple partial seizures with motor, sensory, or autonomic symptoms.
    b. Complex partial seizures.
    c. Partial seizures with secondary generalization.
2. **Generalized seizures—** These are seizures that happen in both hemispheres of your brain side. These seizures tend to cause more severe effects and symptoms.
    a. Absence seizures.
    b. Tonic- clonic seizures.
    c. Other (Myoclonic, tonic, clonic, atonic).

Etiopathogenesis—

- Normal neuronal activity occurs in a non-synchronized manner, with groups of neurons inhibited and excited sequentially during the transfer of information between different brain areas.
- Seizures occur when neurons are activated synchronously. The kind of seizure depends on the location of the abnormal activity and the pattern of spread to different parts of the brain, experimentally, this is known as the paroxysmal depolarizing shift.

- Most inhibitory synapses use the neurotransmitter GABA.
- In secondary epilepsy, loss of inhibitory circuits and sprouting of fibres from excitatory neurons appear to be important for the generation of a seizure focus. In several of the idiopathic epilepsies, genetic studies have identified mutations in ion channels.

Clinical manifestations—

- Cardiac syncope (Arrhythmia).
- Non-Cardiac syncope (vasovagal).
- Breathing problems (dyspnoea).
- Sleep disorders (Narcolepsy).
- Movement disorders (Paroxysmal dyskinesia).
- Metabolic disorders (Hypoglycaemia).
- Migraine's (generally confusion migraine).
- Loss of bowel or bladder control.

Pharmacological managements—

Chemically drugs are classified as-

- Benzodiazepines— ex- clonazepam, lorazepam, diazepam.
- Barbiturates— ex- phenobarbital, desoxyphenobarbital.
- Deoxy barbiturates— ex- primidone.
- Hydantoin— ex-phenytoin, ethotoin.
- Aliphatic carboxylic Acid— ex- valproic acid, magnesium valproate.
- Oxazolidine derivatives— ex- trimethadione, paramethadione.
- Cyclic GABA Analogues— ex- gabapentin, pregabalin.
- Iminostilbene— carbamazepine, oxcarbazepine.
- Other drugs— ex- levetiracetam, parampanel, brivaracetam, lacosamide.

Non-pharmacological management—

- Avoid and discard the all activities which cause/induce the depression, stress, sleep disorders etc.
- Follow and change the diet plans according to own demand or prescription by any RMP.

- Some small extent caffeine, alcohol, nicotinic substance is managing the brain disorder but avoid the ingestion of excessive amounts of these.
- Practice the yoga, meditation, physical exercise regularly. Ventilation is one of the reasons which leads to brain disorders and cardiac disorders also.
- Practice of herbal/natural medicine other than allopathic.
- Do such all activities which makes you happy and cheerful.

Parkinson's Disease

Definition—

- Parkinson Disease (PD) is a neurodegenerative disease marked by a prominent hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra.
- The clinical syndrome of parkinsonism combines diminished facial expression, stooped posture, slowing of voluntary movement, festinating gait (progressively shortened, accelerated steps), rigidity, and a "pill-rolling" tremor.

Etiopathogenesis—

- PD is associated with protein accumulation and aggregation, mitochondrial abnormalities, and neuronal loss in the substantia nigra and elsewhere in the brain.
- Parkinsonism may also result from repeated head trauma or may be a feature of several basal ganglia diseases, including Wilson disease, some cases of early-onset Huntington disease, multiple system atrophy (MSA), and progressive supranuclear palsy.
- Parkinsonism can also result from exposure to certain toxins such as manganese, carbon disulphide, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and carbon monoxide.

Clinical manifestations—

1. **Primary symptoms.**
    - Bradykinesia.
    - Parkinson gait
    - Rigidity
    - Tremors
    - Postural instability.
2. **Secondary symptoms.**
    - Confusion.
    - Memory loss.
    - Anxiety.
    - Depression
    - Difficulty swallowing.
    - Increased sweating.
    - Constipation.

Pharmacological managements—

1. **Drugs acting on cholinergic system—**
    - Anti-histaminic— ex-promethazine, orphenadrine.
    - Central cholinergic— ex- biperiden, trihexyphenidyl, procyclidine.
2. **Drugs acting on dopaminergic system—**
    - Glutamate (NMDA receptor) agonist— ex- Amantadine
    - Catechol-o-methyltransferase (COMT) inhibitors—ex-entacapone.
    - Peripheral decarboxylase inhibitors—ex-carbidopa, benserazide.
    - Dopaminergic agonists—ex- bromocriptine, ropinirole, piribedil.
    - MAO-B inhibitors—ex- selegiline, rasagiline, safinamide.
    - Dopamine precursor—ex- levodopa.
3. **Adenosine receptor antagonist**—ex- istradefylline.

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Alzheimer's disease

Definition—

- Alzheimer disease (AD) is the most common cause of dementia in older adults, with an increasing incidence as a function of age.
- The disease usually becomes clinically apparent as insidious impairment of higher cognitive functions.
- As the disease progresses, deficits in memory, visuospatial orientation, judgment, personality and language emerge.

Etiopathogenesis—

- The fundamental abnormality in AD is the accumulation of two proteins (Aβ and tau) in specific brain regions, likely as a result of excessive production and defective removal.
- The two pathologic Indication of AD, particularly evident in the end stages of the illness, are **plaques and tangles.**
- Plaques are deposits of aggregated Aβ peptides in the neuropil, while tangles are aggregates of the microtubule binding protein tau, which develop intracellularly and then persist extracellularly after neuronal death.
- Both plaques and tangles appear to contribute to the neural dysfunction, and the interplay between the processes that lead to the accumulation of these abnormal aggregates is a critically important aspect of AD pathogenesis.

Genetic Evidences— Multiple lines of genetic evidence point to the likely importance of altered Aβ metabolism.

- Mutations in the protein from which Aβ is derived (APP) cause familial AD, as does increased copy number of the APP gene.
- Furthermore, point mutations in proteins that are part of the protease complexes that generate Aβ from APP also give rise to AD.

Clinical manifestations—

- Deficits in memory.
- Lack of enthusiasm.
- Poor or decreased judgement.
- Difficulty in having elaborate thoughts.
- Disorientation in time and space.
- Drastic behaviour changes.
- Problems in speaking, reading and writing.

Pharmacological managements— drugs used as-

- Cholinesterase inhibitors— ex- donepezil, rivastigmine, galantamine.
- NMDA antagonist— ex- memantine

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Stroke

Definition— Stroke is a clinical syndrome characterized by the sudden onset of a focal neurologic deficit that persists for at least 24 hours and results from an abnormality of the cerebral circulation. The incidence of stroke increases with age and is higher in men than in women. Significant risk factors include hypertension, hypercholesterolemia, diabetes, smoking, heavy alcohol consumption, and oral contraceptive use.

Etiopathogenesis— The focal symptoms and signs that result from stroke correlate with the brain area supplied by the affected blood vessel. There are two major categories of stroke, based on pathogenesis: ischemic and haemorrhagic stroke.

1. **Ischemic stroke—** Ischemic strokes result from thrombotic or embolic occlusion of cerebral vessels. Neurologic deficits caused by the occlusion of large arteries result from focal ischemia to the area of brain supplied by the affected vessel and produce recognizable clinical syndromes.
    - Anterior cerebral symptoms— Sensory loss in movement (foot).
    - Middle cerebral symptoms— Aphasia and neglect (dominant and non-dominant) hemisphere.
    - Posterior cerebral symptoms— Sensory loss, ataxia, nerve palsy etc.

Ischemic strokes involving occlusion of small arteries occur at select locations, where perfusion depends on small vessels that are end arteries. Most result from a degenerative change in the vessel, described pathologically as lipohyalinosis, which is caused by chronic hypertension and predisposes to occlusion.

2. **Haemorrhagic stroke—**
    - Epidural and subdural hematomas typically occur as sequelae of head injury. Epidural hematomas arise from damage to an artery, typically the middle meningeal artery, which can be ruptured by a blow to the temporal bone. Blood dissects the dura from the skull and compresses the hemisphere lying below. Initial loss of consciousness from the injury results from concussion and may be transient.
    - Subarachnoid haemorrhage may occur from head trauma, extension of blood from another compartment into the subarachnoid space, or rupture of an arterial aneurysm. Cerebral

dysfunction occurs because of increased intracranial pressure and from poorly understood toxic effects of subarachnoid blood on brain tissue and cerebral vessels.

- Intraparenchymal haemorrhage may result from acute elevations in blood pressure or from a variety of disorders that weaken vessels. The resultant hematoma causes a focal neurologic deficit by compressing adjacent structures.

Clinical manifestations—

- Face dropping
- Sudden vision disturbance.
- Arm or limb weakness.
- Loss of coordination
- Nausea.
- Trouble speaking.
- Sudden confusion and sometime memory loss.
- Tremors also occurs.

Pharmacological managements—

Tissue plasminogen activator (tPA) is the only stroke drug that actually breaks up a blood clot.

- Non fibrin specific— ex- streptokinase, urokinase, Anistreplase.
- Fibrin specific— ex- Alteplase, reteplase, Tenecteplase.

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Migraine

Definition—

- A migraine is a headache that can cause severe throbbing pain or a pulsing sensation, usually on one side of the head and also involving altered regulation and control of afferents, with a particular focus on the cranium. It's often accompanied by nausea, vomiting, and extreme sensitivity to light and sound.
- Current views concerning migraine will be reviewed concluding the disorder is a disturbance in the brain of the subcortical aminergic sensory modulatory systems, in addition to other brainstem, hypothalamic and thalamic structures.

Etiopathogenesis—

- Pathophysiology of migraine should be based upon the anatomy and physiology of the pain-producing structures of the cranium integrated with knowledge of their central nervous system modulation.

It involved/understand by four phases.

1. **Prodromal symptoms**—It is initial symptoms about one or two days before a migraine including constipation, mood changes from depression to euphoria, food cravings, neck stiffness, increased thirst and urination or frequent yawning, difficulty in speaking, reading, and sleeping.
2. **Aura**— Migraine with aura (also called classic migraine) is a recurring headache that strikes after or at the same time as sensory disturbances called aura it is about 5-60 minutes. These disturbances can include flashes of light, blind spots, and other vision changes or tingling in your hand or face.

3. **Migraine attack/Headache**— It is about 4-72 hours. These disturbances can include burning, nausea, vomiting, giddiness, insomnia, anxiety, depressed mood, sensitivity to light, smell, sound.
4. **Postdrome**— It is about 24- 48 hours. These disturbances can include as inability to concentrate, fatigue, depressed mood, euphoric mood, lack of comprehension.

Clinical manifestations—

- Throbbing, drilling, pounding headache.
- Nausea, vomiting, giddiness.
- Sensitivity towards light and sound.
- Pain in only one hemisphere.
- Diarrhoea, constipation, stomach pain.
- Inability to focus on concentrate.

Pharmacological managements—

- Prophylactic— beta blocker, calcium channel blocker, ACE inhibitor etc.
- Abortive—for blocking the pain pathways many drugs are used Example- NSAIDS, ergotamine, sumatriptan and rizatriptan.

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