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An Overview of Pathogenesis of Epilepsy

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Abstract

Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures, which are sudden and abnormal bursts of electrical activity in the brain. Seizures can manifest as various symptoms, including convulsions, altered consciousness, and sensory disturbances. The disorder encompasses a range of types and syndromes, classified based on seizure origin, presentation, and underlying causes. Focal (partial) seizures originate in a specific brain region and may cause localized or widespread effects, while generalized seizures involve both cerebral hemispheres and often lead to loss of consciousness. Epilepsy's pathophysiology is multifaceted, involving intricate interactions between genetic factors, brain development, and neurochemical imbalances. Genetic mutations in ion channels, receptors, and signaling pathways disrupt neuronal excitability and synchronization. Neuroinflammation and immune responses play a role, with evidence of autoimmune encephalitis triggering seizures. Dysfunctional synaptic plasticity, mediated by altered glutamate-GABA balance, contributes to increased seizure susceptibility. Abnormalities in neuronal migration, cortical malformations, and epigenetic modifications further fuel the disorder. Advancements in understanding epilepsy's diverse pathogenic mechanisms offer promising avenues for targeted therapies and interventions

Key-words: epilepsy, pathogenesis, seizures, classification.

Introduction

Seizures are the temporary disruptions of brain function resulting from abnormal, excessive neuronal activity; Epilepsy is a chronic condition of repeated seizures[1]. According to the World Health Organization (WHO), neurological disorders are ranked as the world's leading cause of loss of disability-adjusted life years (DALYs), comprising 10.2% of the total. Epilepsy is the fifth leading cause of neurological-related DALYs lost, behind stroke, migraine, dementia, and meningitis. The incidence of epilepsy is age-dependent, with the highest incidences found in the young and the elderly. Epilepsy is associated with significant comorbidities, mortality, and societal consequences. Diagnosing epilepsy may be difficult due to the complex nature of the disorders, the occurrences of seizures, the timing, and reports from patients and witnesses [2].

The treatment of epilepsy in children is highly individualized at each major step in the management. Despite prompt treatment, approximately 20% of patients will experience recurrent seizure episodes.

During Hippocrates (400 BC), the Greeks were aware that injuries to one side of the brain could cause seizure activity on the opposite side of the body. During those days, the diagnosis of epilepsy was probably much broader than the contemporary definition. Thus it is likely that focal seizures involving a limited brain area were misinterpreted or never diagnosed. It is difficult for physicians to distinguish between episodic loss of consciousness and various types of seizures [3].

The word epilepsy was derived from the Greeks, which meant "to seize upon" or "taking hold of." Our predecessors referred to it as the "falling sickness" or the "falling evil." A first solitary seizure or brief outburst of seizures may occur during medical illness. It indicates that the cerebral cortex has been affected by disease either primarily or secondarily. If the episode is prolonged or repeated every few minutes, this condition is called status epilepticus that may threaten life. Hence a seizure or series of seizure attacks may manifest an ongoing neurological disease that requires special diagnostic and therapeutic measures[4].

Modern neuro-biological analysis of epilepsy was studied by John Hughlings Jackson's work in London during 1860. Jackson postulated that seizures need not involve loss of consciousness but could be associated with localized symptoms such as arms jerking. Jackson also proposed that seizures occurred as "occasional, sudden, excessive, rapid and local discharges from gray matter," and generalized seizure resulted when normal brain

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tissue was invaded by the seizure activity initiated in abnormal focus. Seizures were due to “an excessive and involuntary disorderly discharge of cerebral neurons on muscles.” The discharge may result in a rapid loss of consciousness, alteration of perception or impairment of psychic function, convulsive movements, disturbance of sensation, or some combination of them. His observation was the first formal recognition of partial seizures. Jackson had also observed that seizures began with focal neurological symptoms and progressed to convulsions with loss of consciousness at the onset [3-4].

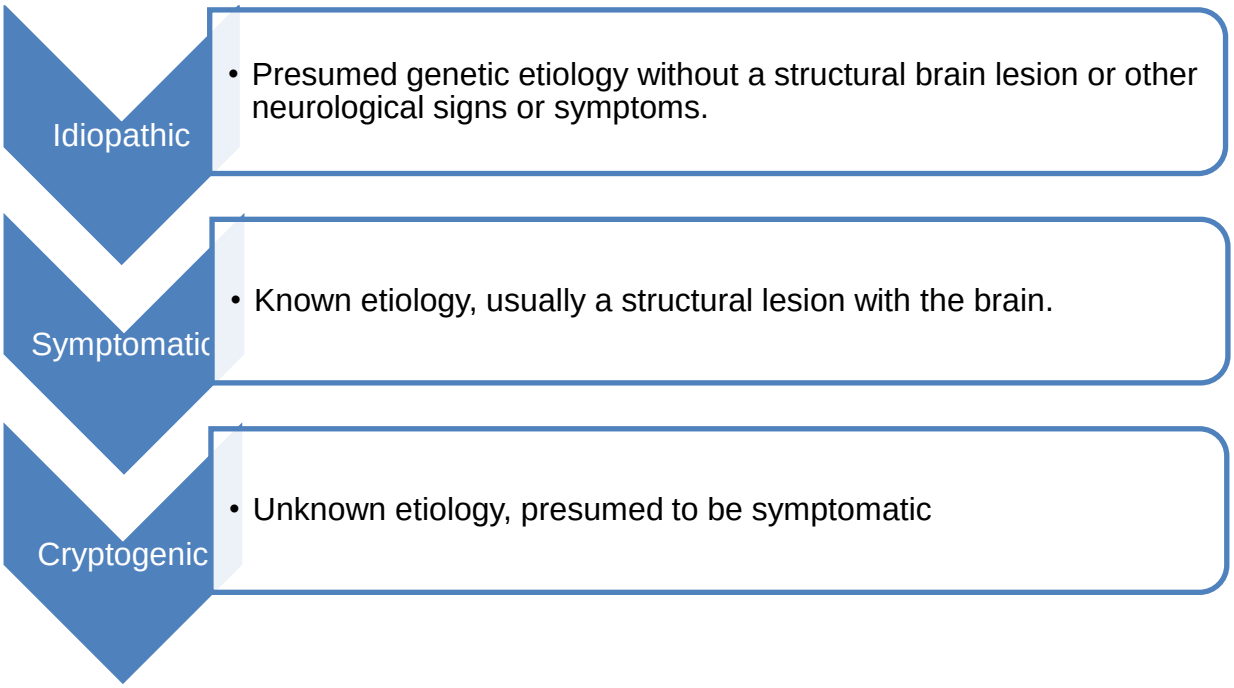
Victor Horsley, in 1886 proposed the first surgical treatment for epilepsy. He cured a patient with focal motar seizures by resecting the cerebral cortex adjacent to a depressed skull fracture. In the 1950s, Wilder Penfield and Herbert Jasper in Montreal proposed the modern surgical treatment for epilepsy[3].

Medical innovation included the first use of antiseizure drug phenobarbital in 1912 by Alfred Hauptmann, the discovery of electroencephalography (EEG) by Hans Berger in 1929, and the development of the anticonvulsant properties of phenytoin by Houston Merritt and Tracey Putnam in 1937[4].

Based on epidemiological studies in the United States, around 3% of all individuals living up to 80 years are diagnosed with epilepsy. The highest incidence rate is observed in young children and the elderly. The signs and symptoms depend on the location and extent of the brain regions that are affected. Over two-thirds of all epileptic seizures begin in childhood[5].

Definition, classification, and its evolution.

The history and advancement of epilepsy classification gained importance in 1960 when Henri Gastaut proposed a classification. Later in 1985, ILAE (International League Against Epilepsy) formulated a “classification of epilepsies and epileptic syndromes.” This was further rectified and revised in 1989 and was widely accepted and followed worldwide. As per the revised guidelines, [6] an epileptic disorder can be classified into:



ILAE commission in 2010 recommended changes to be made in the 1989 classification emphasizing transparent terminology. ILAE in the year 2014 defined Epilepsy as a condition with:

- At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years
- Diagnosis of epilepsy syndrome[7]

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ILAE presented a position paper in 2017 regarding the classification of seizure type, which presented three levels and the presumption that the patient is having epileptic seizures.

- The first level - diagnosis of the seizure type;
- The second level is the diagnosis of epilepsy type, including focal epilepsy, generalized epilepsy, combined generalized-focal epilepsy, and an unknown epilepsy group.
- The third level is looking for a specific syndromic diagnosis, i.e., epileptic syndrome. [8]

The new 2017 classification considers the etiology and comorbidities for every patient with epilepsy at each classification level, enabling early diagnosis and early treatment. This three-level new classification of epilepsy is formulated to cater to different clinical environments and consider the heterogeneity of resources available for diagnosis in different parts of the world.

Table 1: Revised Classification for seizures:

Seizures can be classified into Focal, Generalised, and Seizure of unknown onset[6].

Seizure type	**Features**
Focal Seizures:	
Focal aware	Diverse manifestations determined by the region of cortex activated by the seizure (e.g., if motor cortex representing left thumb, clonic jerking of left thumb results; if somatosensory cortex representing left thumb, paraesthesia of left thumb results), lasting approximately 20-60 seconds.
Focal with impaired awareness	Loss of consciousness lasting for 30 sec to 2minutes, often associated with involuntary movement such as lip-smacking or hand wringing
Focal to Bilateral Tonic-Clonic	Simple or complex focal seizures evolve into a tonic-clonic seizure with loss of awareness and sustained contractions (tonic) of muscles throughout the body, followed by periods of muscle contraction alternating with periods of relaxation (clonic), typically lasting 1-2 minutes.
Generalized Seizures	
Generalized Absence	Abrupt onset of impaired consciousness associated with staring and cessation of ongoing activities, typically lasting less than 30 seconds.
Generalized Myoclonic	A brief (perhaps a second), shock-like contraction of muscles that may be restricted to part of one extremity or may be generalized.
Generalized Tonic-Clonic	As mentioned above, partial with secondarily generalized tonic-clonic seizure is not preceded by a partial seizure.
Unknown Onset	Onset could not be observed, such as when the patient is alone, asleep, or observer could not notice the seizure type as tonic-clonic, atonic or epileptic spasms.

Focal Seizures:

Focal seizures originate in a small group of neurons, and thus the symptoms depend on the location of focus within the brain. Focal seizures were formerly classified as simple partial seizures in which there is no alteration of consciousness or complex partial when there is an alteration of consciousness. A typical focal seizure begins with jerking in hand and progress to clonic movements of the entire arm. Consequently, the patient might lose consciousness, fall to the ground, rapidly extend all extremities (tonic phase), then have jerking in all extremities (clonic phase).

The onset of a focal seizure is often preceded by symptoms called *auras*. Common auras include a sense of fear, a rising feeling in the abdomen, or even a specific odor. Aura is caused by electrical activity originating from the seizure focus and thus represents the initial manifestation of a focal seizure [9].

Generalized Seizures:
Generalized seizures constitute the second main category, and here we can find that seizures are present without an aura or focal seizure and involve both hemispheres from the onset. A generalized seizure can be further divided into convulsive or nonconvulsive types depending on whether the seizure is associated with tonic or clonic movements.

The prototypic nonconvulsive generalized seizure is the typical absence seizure observed in children (also known as petit mal). These seizures begin abruptly and last for less than 10 seconds and are associated with cessation of all motor activity and results in loss of consciousness but not loss of posture. Patients may exhibit mild motor manifestations such as eye blinking but do not fall or have any kind of tonic-clonic movements. Typical absence seizures have very distinctive electrical characteristics on the Electroencephalogram (EEG).

Other generalized seizures can involve only abnormal movements (myoclonic, clonic, or tonic) or sudden loss of motor tone (atonic). The most common is tonic-clonic seizures. These seizures initiate abruptly, often with an aura or cry, as the tonic contraction of the diaphragm and thorax forces expiration. The patient may fall on the ground rigidly with a clenched jaw, loose bladder, or bowel control during the tonic phase and become cyanotic. This phase typically lasts for 30 seconds before evolving into clonic jerking of the extremities lasting 1-2 minutes [10].

Unknown Epilepsy:
In this type, the clinician cannot determine if the epilepsy type is focal or generalized because there is insufficient information available due to various reasons such as no access to EEG or EEG studies give no information, i.e., if it is normal.

Combined generalized and focal epilepsy:
In this type, the patient has both generalized and focal seizures. The diagnosis requires clinical signs and symptoms supported by the finding of typical interictal EEG discharges, which may show both generalized spike-wave and focal epileptiform discharges. E.g.: Lennox-Gastaut syndrome and Dravet syndrome [10].

Prevalence of Epilepsy:
It was estimated that around 70 million populations are suffering from epilepsy worldwide, out of which 12 million patients are observed to be Indian residents. This contributes to nearly one-sixth of the global burden. The overall prevalence (3.0-11.9 / 1,000 population) and incidence (0.2-0.6 / 1,000 population per year) data from recent studies in India on the general population are comparable to the rates of high-income countries despite marked variations in population characteristics and study methodologies. There is a differential distribution of epilepsy among various economic and socio-demographic groups, with higher rates reported for the male gender, rural population, and low socioeconomic status. Secondary epilepsy may be due to conditions like neuro infections, neurocysticercosis, neurotrauma, and birth injuries that have emerged as significant risk factors. Despite its varied etiology, the majority of epilepsy are manageable. Precise determination of etiology is challenging in India due to the poor availability of neuroimaging studies and even lesser access to other investigations such as genetic studies [11].

The Yelandur survey observed that the prevalence of pediatric epilepsy in the Indian population is 3.28-5.71 / 1000 population, while the most recent Uttarakhand survey found a prevalence of 2.27 per 1000 population. The prevalence rate in Karnataka, as shown by two studies at an interval of 20 years, has shown a rising trend from 5.6 to 11.9 per 1,000 for the rural population and 2.5 to 5.7 per 1,000 for the urban population resulting in an overall prevalence varying from 4.6 to 8.8 per 1,000 populations[12].

Epileptogenesis:
Epileptogenesis is a multifactorial phenomenon encompassing the primary process that causes principal neurons to generate their first spontaneous, multiple population spikes containing epileptiform discharges.

This process of spontaneous discharges propagating to other cell populations to produce clinically detectable behavioral signs is called epileptic maturation that follows epileptogenesis. It has been observed that 50% of patients who have suffered a severe head injury develop seizure disorder; however, in most cases, the seizures may become clinically evident only after a few months or years [13].

Primary Mechanism of Epileptogenesis:
Hyper excitable neuronal network is the hallmark of epilepsy which results from increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, alteration in voltage-gated ion channels, or alteration of intra or extracellular ion concentration in favor of membrane depolarization[9].

Under the resting condition, there is high potassium (K+) concentration inside the neuron and a high sodium ion (Na+) concentration outside the cell, creating a transmembrane potential of -60mV. When a stimulus is received at a neuron, it accumulates an electric charge till it crosses the threshold value beyond which an output signal or action potential or spike is generated and transmitted to the adjacent neuron.

This system goes beyond the standard during a seizure, leading to depolarization of neurons and excessive discharge of action potentials. This entire process collectively takes place in a large number of neurons. Strong inputs are generated by neuronal interactions capable of evoking spikes by overcoming the threshold, whereas weak signals fail to evoke. The hypersynchronous discharges might originate from a discrete brain region and then spread to distant regions during a seizure.

At the cellular level, the epileptiform activity consists of sustained neuronal depolarization leading to a burst of action potentials known as paroxysmal depolarizing shift. This bursting action is due to the influx of extracellular calcium ions (Ca^{++}), leading to the opening of voltage-dependent Na^{+} channels, resulting in repetitive action potentials. Subsequent hyperpolarization is mediated by γ-aminobutyric acid (GABA) receptors, Cl^{-} influx, or K^{+} efflux restricting the propagation of bursting activity.

Continuous discharges lead to an increase in extracellular K^{+}, which reduces the extent of hyperpolarizing outward K^{+} currents, tending to depolarize neighboring neurons. It also causes the accumulation of Ca^{++} in presynaptic terminals leading to enhanced neurotransmitter release [9].

Role of Glutamate Receptors in Epileptogenesis:
Excitatory transmission primarily mediated by glutamate neurotransmitter, which is released from pyramidal neurons, leads to depolarization and excitation of target neurons through ionotropic receptors N-methyl-D-aspartic acid (NMDA) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, and kainic acid receptor.

Depolarization activates the NMDA subtype of glutamate receptors, leading to more Ca++ influx and neuronal activation, contributing significantly to enhanced excitatory activity. NMDA receptors are tetramers that have a significant role in epilepsy. Hence abnormal regulation of NMDA receptor-mediated activity can be a significant contributor to epileptogenesis [9].

Role of GABAergic Neurotransmission in Epileptogenesis:
Insights into the mechanism of seizures suggest that increasing GABA-mediated synaptic inhibition would decrease neuronal excitability and raise the seizure threshold. Several drugs are thought to inhibit seizures by regulating GABA-mediated synaptic inhibition through action at specific sites of the synapse.

Glutamate neurons synapse onto both glutamate as well as GABAergic neurons. The glutamate-induced seizure generation could be due to excessive glutamate receptor activity or increased release of GABA through depolarization of GABAergic neurons. The principal post-synaptic receptor of synaptically released GABA is termed as $GABA_A$ receptor. Activation of the GABA receptor inhibits the post-synaptic cell by increasing the inflow of Cl^{-} ions into the cell, which tends to hyperpolarize the neuron[9].

Role of Cell Surface Receptors and Downstream Signaling pathways in Epileptogenesis:
Neurotrophins such as brain-derived neurotrophic factor (BDNF) and its downstream signaling pathway have been implicated in epileptogenesis. Seizure-induced increase of BDNF expression and enhanced activation of its cognate receptor tropomyosin receptor kinase B (TrkB) is demonstrated in animal models of Temporal lobe epilepsy (TLE).

Overexpression of BDNF leads to increased seizure susceptibility or severity, and conditional knockout of TrkB eliminated epileptogenesis in animal models of epilepsy. Also, in response to mossy fiber activation, estrogen enhances epileptiform activity in the CA3 pyramidal cells in female rats, and the Trk antagonist blocks this

effect. These findings strongly support the contribution of BDNF and TrkB seizure susceptibility and epileptogenesis[14].

Role of Genetics and Epigenetics in Epileptogenesis:
Epilepsy is a group of heterogeneous disorders caused by interactions between many genes and environmental factors. Genetic epilepsies due to single-gene mutations or defined structural chromosomal aberrations such as microdeletions are very rare.

Familial epilepsies include febrile seizures, generalized epilepsy with febrile seizure plus (GEFS+), and severe myoclonic epilepsy of infancy (or Dravet disease). The GEFS+ is associated with mutations in Sodium voltage-gated channel alpha subunit 1 (*SCN1A)*, Dravet syndrome is associated with mutations in (*SCN1A*), and benign familial neonatal convulsions are associated with mutations in Potassium voltage-gated channel subfamily Q (*KCNQ2* and *KCNQ3).* Epilepsy can also result from a mitochondrial inheritance, such as mitochondrial encephalopathy, lactic acidosis, stroke-like episode syndrome, and myoclonus epilepsy with ragged-red fiber syndrome. The aberration of chromosome structure is another cause of epilepsy syndromes, such as ring chromosome 20 and ring chromosome 17 [15]. Genetic research has been instrumental in understanding the basis of epilepsy. Mutations in certain genes have been identified as risk factors for epilepsy. For instance, mutations in genes like SCN1A and SCN2A, which encode voltage-gated sodium channels, have been associated with various epilepsy syndromes, including Dravet syndrome. DEPDC5 mutations have been linked to familial focal epilepsy. These genetic discoveries help in understanding the molecular mechanisms underlying epilepsy development[16].

Epigenetic alterations, including histone tail modifications, DNA methylation patterns, microRNA (miRNA) expression, and transcription factor recruitment, are associated with epilepsy. Recent studies reported the association of transcription factors like repressor element 1-silencing transcription factor, methyl-CpG binding protein 2(MeCP2), and cAMP response element-binding element (CREB) with epileptogenesis. These transcription factors may modulate the expression of genes involved in epigenetic modifications leading to altered neuronal excitability and neuronal network organization[15].

miRNAs are key regulatory molecules in cells controlling protein levels in the pathogenesis of seizure-induced epilepsy in both animal models and humans. Most of the altered miRNAs, including miR-23a, miR-34a, miR-132 and miR-146a, miR-34a, miR-21, miR-29a, and miR132, were shown to contribute to inflammation and neuronal death, leading to epileptogenesis [15].

Epigenetic modifications are chemical changes that alter gene expression without changing the DNA sequence. DNA methylation and histone modifications are examples of epigenetic processes. Aberrant epigenetic changes can lead to altered gene expression patterns, affecting the balance between excitatory and inhibitory neurotransmission and contributing to epilepsy development.

There is growing recognition of the role of the immune system in epilepsy. Autoimmune encephalitis involves an autoimmune response against neuronal antigens, leading to inflammation and seizures. Antibodies targeting NMDA receptors are an example of this. The link between the immune system and epilepsy has led to the exploration of immune-modulating therapies for refractory epilepsy cases[17].

Neuroinflammation, characterized by increased activation of immune cells in the brain, can disrupt the balance between excitatory and inhibitory signaling. Inflammatory molecules can impact synaptic plasticity, making neurons more excitable and prone to generating seizures. This has highlighted the potential of targeting neuroinflammatory pathways for novel anti-seizure strategies[18].

Microglia and astrocytes, the brain's resident immune cells, play crucial roles in maintaining brain homeostasis. Dysregulated activation of microglia and altered astrocyte function can contribute to epilepsy. Microglial activation can lead to the release of pro-inflammatory molecules, exacerbating neuroinflammation. Dysfunctional astrocytes may impair neurotransmitter clearance and alter the extracellular environment, promoting seizures[19].

Many epilepsy cases are associated with structural brain abnormalities that arise during early brain development. Cortical malformations, such as focal cortical dysplasia, disrupt the normal organization of brain

tissue, leading to abnormal circuitry and increased seizure susceptibility. Disruptions in neuronal migration during fetal development can also contribute to epilepsy[20].

Conclusion

These points collectively underscore the complex interplay of genetic, immune, inflammatory, and developmental factors in the pathogenesis of epilepsy. Research in these areas has provided insights into potential therapeutic targets and strategies for treating epilepsy and related disorders.

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