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Epilepsy: From Ancient Stigma to Precision Medicine in Modern Neurological Care

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ABSTRACT

Epilepsy is a chronic, globally prevalent neurological disorder, affecting an estimated 50 to 70 million people worldwide. Defined operationally by the International League Against Epilepsy (ILAE) as a brain disease characterized by a tendency toward frequent, unprovoked seizures, epilepsy carries a significant burden, accounting for 0.7% of the world's illness burden in 2010. This review synthesizes current knowledge regarding epilepsy's complex historical perception, detailed classification based on seizure onset, and diverse etiologies, which include genetic, structural, metabolic, infectious, and immunological causes. Diagnosis relies fundamentally on clinical history, complemented by electroencephalogram (EEG) and advanced neuroimaging (MRI, PET, SPECT). While pharmacological agents achieve seizure freedom in about 70% of patients, approximately one-third develop drug-resistant epilepsy (DRE). For DRE, non-pharmacological interventions such as surgery, neurostimulation (VNS, DBS), and dietary therapies (Ketogenic Diet) are crucial alternatives. Future treatment is moving toward precision medicine, utilizing genetic data (pharmacogenomics) to tailor treatments and mitigate adverse drug reactions. Addressing the profound psychosocial stigma, which is often linked to psychiatric comorbidities like depression and anxiety, remains a critical component of holistic epilepsy management.

Keywords: Epilepsy, Seizure, Anti-epileptic Drugs (AEDs), Classification, Drug-Resistant Epilepsy (DRE), Neurostimulation, Stigma, Pharmacogenomics, Ketogenic Diet.

INTRODUCTION

Epilepsy is recognized as one of the most common and serious long-term neurological conditions globally, affecting 50 to 70 million individuals across various demographics. Although 10% of the population may experience a single seizure, epilepsy is distinguished as a more severe disorder characterized by a propensity for unprovoked seizures. The term "epilepsy" originates from the Greek word *epilepsia*, meaning "to be seized" or "to take hold of," reflecting ancient views that seizures resulted from supernatural forces, such as demon possession. This historical association with mystical or evil spirits led to intense stigma, causing isolation and mistreatment that continues to pose a serious problem today, particularly in developing nations where about 90% of people with the condition reside.

The International League Against Epilepsy (ILAE) defines an epileptic seizure as a transient occurrence of symptoms or signs resulting from excessive, abnormal, or synchronous neuronal brain activity. Operationally, epilepsy is defined as a brain disease characterized by a specific epilepsy syndrome diagnosis, or at least two unprovoked seizures occurring more than 24 hours apart, or one unprovoked seizure with a high likelihood (at least 60%) of subsequent seizures over the following decade. This contemporary definition differentiates the persistent condition from isolated seizures caused by temporary circumstances. The burden of the illness is substantial, encompassing physical risks, psychosocial impairment due to stigma, negative effects of long-term medication, and an increased risk of early mortality. Epilepsy accounted for 0.7% of the world's illness burden in 2010, predominantly impacting low- and middle-income nations. This review seeks to comprehensively explore the etiology, diagnosis, management, and future therapeutic directions for this complex neurological disorder.

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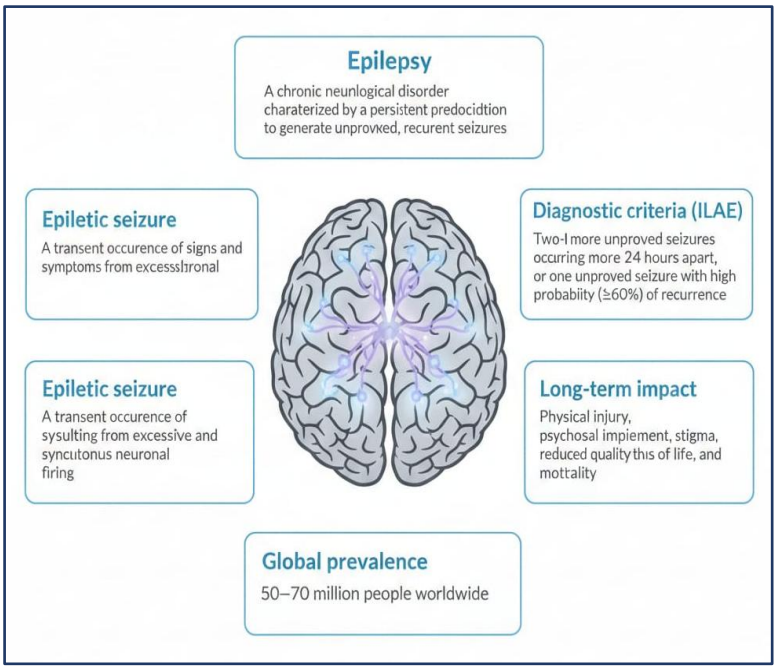

Fig.no.1: Conceptual Illustration Of Epilepsy & It's Core Characterstics.

Methodology

This thorough review summarizes the current understanding of epilepsy, drawing on a large existing body of research concerning biomolecular mechanisms, causes, diagnosis, and treatment. The methodology was systematic and comprehensive, ensuring a broad and fair review without conducting new empirical research.

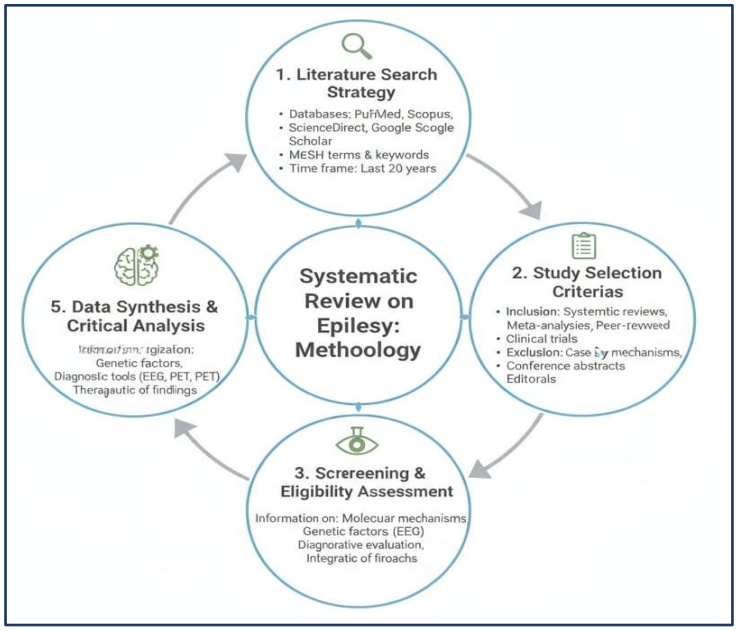

Fig.no.2: Methodological Framework for the Systematic Review of Epilepsy.

Literature Searches: A thorough literature search was executed using prominent scientific databases, including PubMed, Scopus, Science Direct, and Google Scholar. Keywords combined with Medical Subject Headings (MeSH) were used to identify relevant clinical trials, reviews, fundamental research papers, and publications. The search primarily focused on works published within the last 20 years to ensure coverage of recent developments, though foundational historical papers were also included.

Inclusion and Exclusion Criteria: Priority was given to meta-analyses, systematic reviews, peer-reviewed publications, and pivotal clinical trial reports. Included sources provided substantial insights into pathophysiology, etiology, classification, diagnostic procedures (EEG, MRI, PET, SPECT), and both conventional and novel therapy modalities. All selected articles were in English. Case reports, conference abstracts, and editorials were generally excluded unless they offered novel insights not covered in full-length publications.

Data Extraction and Synthesis: Data was methodically extracted and arranged into thematic groups relevant to the review's main topics, such as molecular mechanisms, genetic factors, advancements in diagnostic technology, and therapeutic approaches. The gathered information was critically analyzed and synthesized to create a cohesive narrative, with the goal of presenting a comprehensive overview that transcends a basic summary by linking disparate findings and emphasizing significant trends in the field.

Epidemiology

Epilepsy is a chronic and important neurological disorder that can affect individuals of any age, race, or gender, characterized by a tendency for unprovoked seizures.

Prevalence and Incidence: Globally, approximately 1% of people have epilepsy. Estimates suggest about 65 million people worldwide have the disorder, with approximately 3.4 million epileptics in the United States. New cases of epilepsy are often identified at a rate of roughly 50 new cases per 100,000 persons every year, totaling an estimated 150,000 new cases annually in the US.

Age of Onset: The vast majority of epilepsy cases, about 75%, begin in childhood, partly due to the developing brain's increased vulnerability to seizures. A second peak in the age of onset occurs in the senior population, likely due to the increased prevalence of age-related brain diseases like cerebrovascular lesions. Different epilepsy syndromes have distinct onset periods: Juvenile Myoclonic Epilepsy (JME) typically begins between ages 10 and 25 (around puberty), Childhood Absence Epilepsy (CAE) starts between ages 4 and 10, and West Syndrome (infantile spasms) primarily begins within the first year of life, peaking between 4 and 6 months.

Syndrome-Specific Prevalence: Juvenile Myoclonic Epilepsy (JME) is a common syndrome, estimated to account for 2.8% to 11.9% of all epilepsies. Among genetic generalized epilepsies, JME is highly prominent, making up 26.7% of this specific subgroup. Recent large-scale investigations suggest a preponderance of females in JME populations, with one dataset reporting that 61% of JME patients were female.

Risk of Mortality: Individuals with epilepsy face an increased risk of premature death, up to three times higher than the general population, with this risk being most noticeable in low- and middle-income nations and rural locations. Preventable causes contribute to a sizable percentage of epilepsy-related fatalities, including extended seizures (status epilepticus), burns, drowning, and falls. When seizures are adequately controlled, epilepsy generally does not significantly affect life expectancy, although inadequate seizure control severely impacts quality of life.

Classification

The ILAE classification system arranges seizures based on their onset. The operational definition of epilepsy is a brain disease diagnosed by one of three criteria: a specific epilepsy syndrome, two or more unprovoked seizures more than 24 hours apart, or one unprovoked seizure with at least a 60% probability of recurrence.

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Seizure Types:

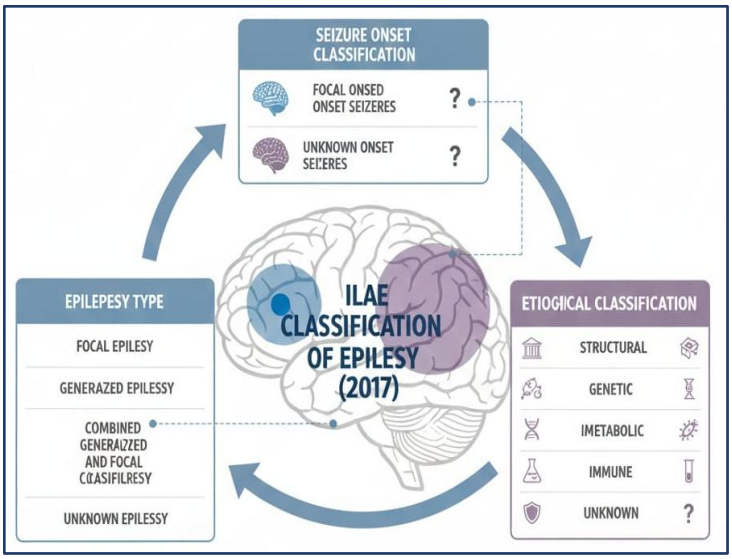

Fig.no.3: ILAE Classification Of Epilepsy

Focal Onset Seizures: These originate within the networks of one cerebral hemisphere and are classified based on whether awareness is compromised. Clinical symptoms immediately reflect the affected brain regions; for example, motor cortex discharges cause convulsions, and reticular formation involvement can lead to loss of consciousness. They may manifest as motor symptoms (tonic posture, jerking), sensory phenomena (visual hallucinations, tingling), autonomic changes, or mental experiences (fear, *déjà vu*).

Generalized Onset Seizures: These rapidly activate bilateral networks and seem to begin in both hemispheres simultaneously. Types include tonic-clonic (formerly *grand mal*), absent (formerly *petit mal*), myoclonic (short muscular jerks), or atonic (*drop attacks*).

Epilepsy Syndrome Diagnosis: The diagnostic process aims to determine the specific epileptic syndrome, which is a distinctive cluster defined by seizure types, imaging features, EEG patterns, age of onset, and comorbidities. Common pediatric syndromes include West syndrome, Dravet syndrome, Lennox-Gastaut syndrome, and benign Rolandic epilepsy.

Etiology & Pathophysiology

Epilepsy is not a single disease but rather a group of syndromes resulting from diverse underlying brain dysfunctions.

Pathophysiology (Molecular Mechanism): A seizure fundamentally represents a critical disruption in the balance between excitatory and inhibitory forces within the central nervous system. The key players are the primary excitatory neurotransmitter, glutamate, and the primary inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). An epileptic event is triggered by either a decrease in inhibitory activity or an enhancement of excitatory synaptic activity. This imbalance results in the characteristic hypersynchronous firing of a neuronal population, which manifests clinically as a seizure. Many anti-epileptic drugs (AEDs) function by modulating these systems, such as by enhancing GABA-mediated inhibition or blocking voltage-gated sodium or calcium channels.

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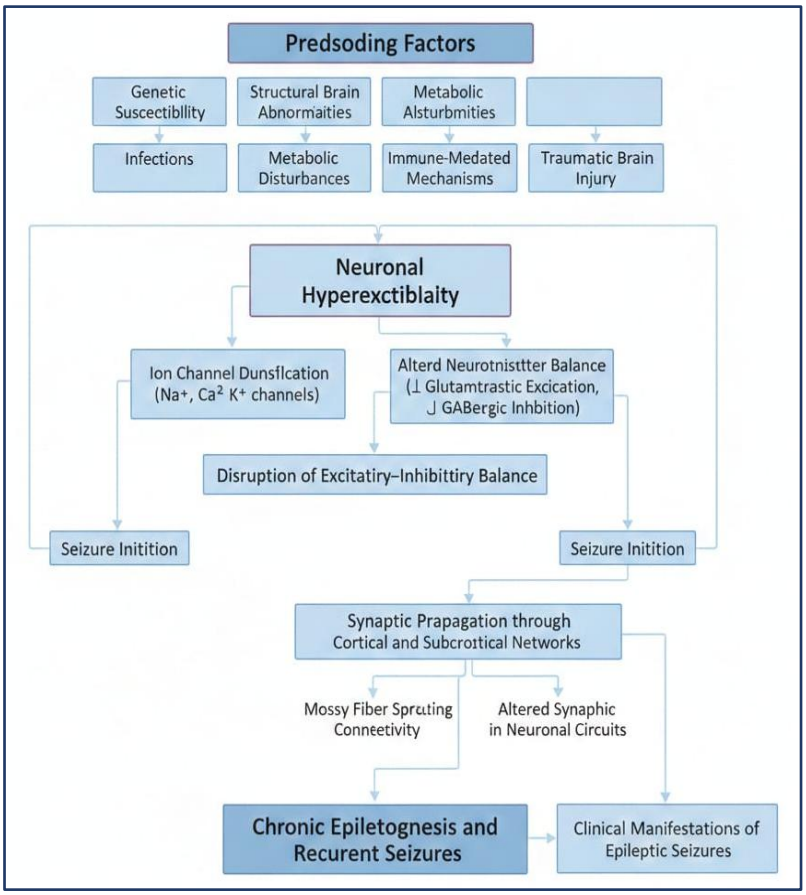

Fig.no.4: Pathophysiology Of Epilepsy.

Etiological Classification (ILAE): The ILAE organizes the diverse causes of neuronal hyperexcitability into six broad categories:

Genetic: Significant contributors, ranging from single-gene mutations (e.g., in potassium channel genes leading to benign familial neonatal epilepsy) to complex polygenic predispositions (e.g., Juvenile Myoclonic Epilepsy). Advances like whole exome sequencing have clarified the genetic makeup of severe conditions such as Dravet syndrome.

Structural: Acquired or congenital brain abnormalities visible on neuroimaging that are causally linked to seizures. Examples include acquired brain damage from tumors, head trauma (TBI), stroke, or infections like neurocysticercosis. Cerebrovascular disease is the cause in about half of all new epilepsy cases in older adults.

Infectious: Leading cause globally, particularly in developing countries, encompassing central nervous system infections like cerebral malaria, viral encephalitis, neurocysticercosis, and tuberculosis.

Metabolic: Important to identify due to specific treatment implications, such as pyridoxine-dependent seizures or cerebral folate deficiency, which respond to targeted therapies.

Immune: Increasingly recognized, such as anti-NMDA receptor encephalitis, which may respond to specific immunotherapies.

Unknown: The cause of epilepsy remains unknown in a significant proportion of cases.

Diagnostic Approaches

The diagnostic paradigm combines clinical assessment with advanced technology to locate the seizure focus and determine the etiology.

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Clinical Evaluation: A thorough clinical history, gathered from the patient and eyewitnesses, remains the single most important diagnostic tool.

Electroencephalogram (EEG): The EEG is essential for epilepsy diagnosis as it records the brain's electrical activity. It can detect distinctive epileptiform discharges even during the interictal interval (between seizures). Activation techniques, including sleep deprivation, hyperventilation, and photic stimulation, are often employed to enhance diagnostic output. Long-term video-EEG monitoring is crucial in complex cases for correlating clinical behaviors with electrical activity, especially when differentiating epileptic seizures from psychogenic non-epileptic seizures (PNES).

Neuroimaging: Neuroimaging has fundamentally transformed diagnosis. Magnetic Resonance Imaging (MRI) is superior to computed tomography (CT) for identifying subtle structural brain lesions, such as cortical abnormalities, tumors, or hippocampal sclerosis, that frequently cause seizures. Advanced functional imaging techniques, including Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), are used to provide functional information on blood flow or metabolism, which aids in precisely locating the epileptogenic zone, especially for patients being considered for surgery.

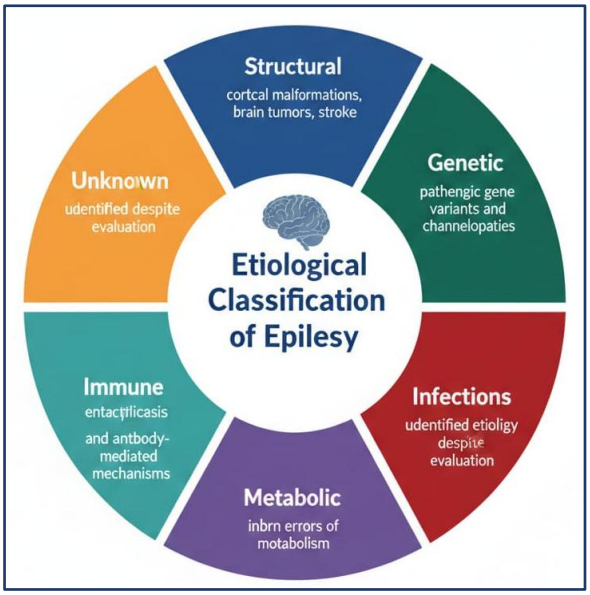

Fig.no.5: Etiological Classification Of Epilepsy.

Pharmacological Management

The primary objective of epilepsy management is to achieve complete seizure control with minimal adverse effects, thus maximizing the patient's quality of life. Anti-epileptic drugs (AEDs) are the mainstay of treatment and help approximately two-thirds (about 70%) of patients achieve seizure freedom.

Treatment Initiation and Monotherapy: Treatment usually begins with a single AED (monotherapy) at a low dose that is progressively increased to determine the lowest effective dose. About half of patients achieve seizure control with the initial AED. The initial AED choice is customized based on the patient's comorbidities, age, and, crucially, the epilepsy and seizure type. For example, ethosuximide is effective for absence seizures, whereas carbamazepine can exacerbate myoclonic seizures.

Agent Selection and Specific Considerations:

Valproic Acid is highly successful for generalized epilepsies but is severely restricted in women of childbearing potential due to the possibility of teratogenicity, including impaired postnatal cognitive development and a higher rate of major congenital malformations in offspring.

Elderly Patients often show a good treatment response, with seizures resolving in up to 96% of cases. However, dosing must start significantly lower (e.g., 1/4 to 1/2 of the usual adult dose) and be titrated gently due to slower drug metabolism. Non-enzyme-inducing AEDs (such as lamotrigine, levetiracetam, and lacosamide) are preferred, as enzyme-inducing AEDs (like carbamazepine,

phenobarbital, and phenytoin) can reduce the efficacy of other necessary medications (e.g., anticoagulants, statins) and may contribute to osteoporosis.

Drug Resistant Epilepsy (DRE)

Approximately one-third (more than 30%) of patients acquire DRE, also known as pharmacoresistant or refractory epilepsy. DRE is defined as the failure of two appropriately chosen and tolerated AEDs to achieve long-term seizure independence.

Management Challenges: DRE is associated with higher rates of morbidity and mortality. For these patients, transitioning to polytherapy (the use of multiple AEDs) is an option, but there is less than a 15% chance of achieving seizure independence with additional AEDs. Therefore, non-pharmacological therapies, particularly epilepsy surgery, must be seriously investigated for DRE patients. Referral to a specialized, comprehensive epilepsy centre is crucial to optimize medical therapy and consider alternatives for pharmacoresistant epilepsy.

Non-Pharmacological Management

Non-pharmacological interventions are essential for patients with drug-resistant focal epilepsy and offer the best chance for seizure control.

Epilepsy Surgery: For carefully selected individuals, surgery can be curative, particularly for drug-resistant focal epilepsy. The procedure involves resecting, disconnecting, or removing the epileptogenic zone (the seizure focus). Pre-operative evaluation is rigorous, utilizing video-EEG monitoring and neuroimaging (MRI, PET, SPECT) to precisely locate the seizure focus. Surgery has proven far more effective than continuous medication; in one randomized trial, 58% of surgical patients stopped having incapacitating seizures, compared to 8% in the medicinal group.

Neurostimulation: For patients not suitable for resective surgery, neurostimulation can reduce seizure frequency and improve quality of life, though it rarely results in complete seizure freedom.

Vagus Nerve Stimulation (VNS): A device is implanted to send regular electrical impulses via the vagus nerve in the neck, which can reduce seizure frequency by over 50% in nearly half of the individuals.

Deep Brain Stimulation (DBS) and Responsive Cortical Stimulation (RCS): These are more targeted techniques involving positioning electrodes in specific brain regions (DBS of the thalamus's anterior nucleus) or directly on the seizure focus (RCS) to interrupt abnormal electrical activity.

Dietary and Alternative Therapies:

Ketogenic Diet: This high-fat, low-carbohydrate diet is a successful treatment, especially for drug-resistant childhood epilepsies and metabolic disorders like glucose transporter type 1 deficiency syndrome. In one trial, 38% of children on the diet experienced a seizure reduction of more than 50%, compared to 6% of controls.

Medicinal Cannabis (Cannabidiol or CBD): CBD, a non-psychoactive component, has been used to treat certain severe epilepsy disorders, with a randomized experiment showing it dramatically decreased convulsive seizure frequency in patients with Dravet syndrome.

Psychological Aspects

The impact of epilepsy extends far beyond the physical seizures, imposing a heavy psychosocial burden that profoundly affects mental health and quality of life. The most pervasive challenge is the stigma associated with the condition, which is often cited as being more difficult to overcome than the seizures themselves. A meta-analysis revealed that over one in three people with epilepsy (35%) experience some form of stigma, which was found to be higher in studies from Africa (40%) compared to Asia (28%).

This pervasive stigma is strongly linked to a higher prevalence of psychiatric comorbidities. Rates of major depression (23.1%) and anxiety (20.2%) are significantly higher in people with epilepsy compared to the general population. Stigma itself is a powerful predictor of depression. The stigmatization load can also worsen functional neurological symptoms, such as psychogenic non-epileptic seizures (PNES). Furthermore, stigma has been linked to negative outcomes, including non-adherence to medication, lower marriage rates, and disrupted school attendance. This necessitates a holistic care model that integrates screening for mental health issues and stigma into routine epilepsy management.

Discussion Section

Epilepsy is one of the oldest known neurological conditions, first documented over 3,000 years ago in ancient Babylon, with seizures historically ascribed to attacks by gods or demons. It was Hippocrates, around 400 B.C., who first correctly proposed that epilepsy was a brain disorder. Modern science recognizes epilepsy as a chronic neurological disorder characterized by hypersynchronous electrical discharges of neurons, impacting quality of life not only through seizures but also via related cognitive, behavioral, and psychosocial issues.

Classification and Diagnosis Evolution: Effective classification is crucial for determining prognosis and selecting appropriate treatment. The ILAE classification has evolved, moving from the 1981 framework (partial, generalized) to the 2017 revision, which replaced "simple partial" and "complex partial" with "focal aware" and "focal impaired awareness" seizures, respectively. Furthermore, the term "secondarily generalized" was modified to "focal to bilateral tonic-clonic" to more accurately reflect seizure progression. This modern, three-tiered diagnostic approach—identifying seizure type, epilepsy type, and epileptic syndrome—underlines the need for comprehensive diagnostic workup, utilizing key tools like the essential EEG and superior MRI imaging, which is invaluable for locating subtle structural lesions such as hippocampal sclerosis.

Management and Future Directions:

While AEDs successfully control seizures for the majority, the existence of Drug-Resistant Epilepsy (DRE) in one-third of patients necessitates alternative strategies. For DRE, epilepsy surgery offers a potentially curative option for suitable candidates, while neurostimulation techniques (VNS, DBS, RCS) and dietary measures like the Ketogenic Diet provide vital seizure frequency reduction.

The future of epilepsy care is centered on precision medicine, moving beyond symptom suppression to targeting underlying causes. Genetic advancements allow for tailored therapies, such as avoiding sodium channel-blocking medications in epilepsies caused by *SCN1A* mutations. Pharmacogenomics plays an increasingly important role, highlighted by the recommendation for genetic screening (e.g., for the HLA-B*1502 allele) in certain populations before prescribing carbamazepine to predict life-threatening skin reactions. The validation of biomarkers (genetic, imaging, or electrophysiological measures) is crucial to predict drug response, identify high-risk individuals, and effectively monitor treatment, replacing the current reliance on trial-and-error methods. Finally, addressing the pervasive psychosocial stigma is essential for a holistic approach that improves patient outcomes and adherence to treatment.

Conclusion

Epilepsy care has undergone significant evolution, shifting toward a multifaceted and personalized approach. Antiseizure medications (ASMs) remain central, achieving seizure control in roughly 70% of individuals. For the substantial minority with DRE, advanced diagnostics, including high-resolution MRI, PET, and SPECT, enable the precise identification of seizure origins, thereby increasing the safety and efficacy of surgical options like focal resection. Furthermore, neuromodulation therapies, such as VNS, DBS, and RNS, offer powerful alternatives by modulating neural circuits to reduce seizure frequency. Innovative, targeted therapies, including the ketogenic diet for metabolic epilepsies and cannabidiol (CBD) for severe syndromes like Dravet syndrome, represent a move toward precision medicine. This integration of genetic insights with tailored pharmacological and non-pharmacological interventions promises a brighter future by improving seizure control and the overall quality of life for millions of people worldwide living with this challenging neurological disorder.

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