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Overview of Seizure and Epilepsy Syndromes and Their Multidisciplinary Management

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ABSTRACT

Abnormal hyperexcitable electrical discharges of the cerebral cortex lead to the disturbance between the inhibitory and excitatory balance of the neural network. Seizure is caused by four main mechanisms, including metabolic, structural, inflammatory, and infectious mechanisms. Seizures are classified as partial and generalized based on the isolation in a specific area in one brain hemisphere or passing through the nerve fibers and spreading to the other hemisphere as well. Epilepsy is defined as the occurrence of more than two unprovoked and unpredicted repeated seizures. Epilepsy affects more than three million individuals in the United States and approximately 50 million individuals worldwide. Epilepsy may be of an unknown origin, while it could also be associated with certain syndromes. General and specific approaches to seizure treatment encompass a wide range of factors. The general approach should be focused on reassurance and raising the awareness of the patients and their family, and the specific treatment is focused on utilizing pharmacological and surgical approaches. In general, the surgical approaches used for medication-refractory seizures are both palliative and curative, showing promising results if the epileptogenic area is localized using a multidisciplinary approach via live video-electroencephalography monitoring or direct intracranial electrode placement. In addition, the utilization of live modern imaging modalities coupled with surgical approaches could enhance the success rate of the treatment and increase the seizure-free duration.

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Introduction

Abnormal hyperexcitable electrical discharges of the cerebral cortex lead to the disturbance between the inhibitory and excitatory balance of the neural network. The increased release of gamma-aminobutyric acid (GABA) from the interneuron network into the post-synaptic space induces an inhibitory post-synaptic potential (IPSP) through the GABA-A chloride channel, along with the indirect inhibition of the excitatory particles that are mediated by the GABA-B channel. Therefore, the reduced inhibition of the GABA-A and GABA-B channels, as well as the defective intracellular calcium buffering, are the three main mechanisms associated with seizure provocation through an inhibitory pattern.

Defective activation of GABA-secreting neurons is associated with the higher prevalence of seizures (1,2). Furthermore, the increased activation of N-methyl-D-aspartate (NMDA) receptors increases the synchrony between neurons due to

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ephaptic interaction and increased synchrony and activation due to the recurrent excitatory collateral neural network, which are the major causes of the hyperexcitation patterns leading to seizure provocation (3).

NMDA receptor stimulation is mediated by glutamate, resulting in the excitatory post-synaptic potential (ESPS) in the post-synaptic neurons. The described mechanisms in the localized cortical or subcortical areas of one brain hemisphere may manifest as focal (partial) seizures, along with epileptiform and non-epileptiform wave patterns on the electroencephalogram (EEG). The epileptiform waves characterize focal seizures with spikes and sharp waves, while alterations in normal rhythms in the patients with preexisting brain abnormalities may be in favor of non-epileptiform waves in focal seizures (4).

On the other hand, generalized seizures are caused by cortical and subcortical triggers or abnormal neuronal structures. Moreover, animal studies regarding generalized seizures have indicated lateral geniculate body, ascending pathways through the mammillary bodies, and anterior thalamus and substantia nigra, which contain containing nigrotectal GABAergic projections and locus coeruleus as the potential brainstem structures that are responsible for the provocation of generalized seizures (5).

Epilepsy is defined as the occurrence of more than two unprovoked and unpredicted seizures. Epilepsy affects more than three million individuals in the United States and approximately 50 million individuals worldwide. Epilepsy may be of an unknown origin, while it has been associated with certain syndromes, such as juvenile myoclonic epilepsy and Lennox-Gastaut syndrome (LGS) (6).

Seizure is caused by four main mechanisms, including metabolic, structural, inflammatory, and infectious mechanisms. The metabolic causes of epilepsy are altered sodium and glucose, phenylketonuria, drug poisoning, kidney and liver failure, alcohol withdrawal, and snake bites. The underlying structural abnormalities associated with epilepsy could be classified as traumatic brain injury, congenital brain defects, and space-occupying lesions of the brain (e.g., tumors and hemorrhage). Among the other causative agents of seizure provocation are inflammatory processes (e.g., cerebral vasculitis) and infections spreading to brain parenchyma or meninges (7).

In giant-cell arteritis (GCA), large- and medium-sized arteries are influenced by female preference, causing arterial narrowing in the central nervous system (CNS) and leading to various neurological symptoms, including new-onset constant headaches, jaw claudication, and visual symptoms, as well as rare cases of stroke and seizures as described by Silbert et al. (8). As another variant of GCA, patients with Takayasu arteritis may exhibit neurological symptoms, ranging from mild lightheadedness to seizures in severe cases. The involvement of the CNS in polyarteritis nodosa may cause peripheral and central neuropathy, manifesting as seizures. Additionally, Nishino et al. (9) and Fauci et al. (10) have described neurological involvement in 22-33.6% of the patients diagnosed with granulomatosis with polyangiitis (Wegener's granulomatosis), manifesting as ischemic stroke, hemorrhage, encephalopathy, and seizures.

In this regard, Sehgal et al. (11) have reported the involvement of the CNS in the form of intracranial hemorrhage and subsequent seizures in 6-8% of the patients with Churg-Strauss syndrome, which is the rare necrotizing vasculitis of the small vessels. Moreover, more than 30% of the patients diagnosed with Behcet's disease have been reported to gradually develop neurological involvement after an average of five years. On the other hand, Neuro-Behcet (NB) may manifest as parenchymal NB with motor tract signs, strokes, and headaches, while epileptic seizures may appear as the solo manifestation of NB as stated by Chroni et al. (12).

Literature Review

Types of Seizures and Epilepsy

Partial seizures are classified into three main categories. Simple partial seizures may manifest as motor, somatosensory, autonomic, and psychiatric symptoms. Complex partial seizures may appear as simple partial seizures with the loss of consciousness (LOC) and may present as LOC at the onset. Additionally, partial seizures may become secondary generalized with three distinct patterns, including simple partial seizures developing to generalized seizures, complex partial seizures developing to generalized seizures, and simple partial seizures first developing to complex partial seizures and progressing to generalized patterns (13).

Generalized seizures are classified as absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures. Absence seizures are characterized by sudden onset attacks, which interrupt ongoing activities and may manifest as a blank stare in the brief upward rotation of the eyes lasting for a few seconds to half a minute, disappearing as rapidly as the onset. Through hyperventilation, absence seizures will seize the process with mild eyelid clonus and the slight loss of neck muscle tone and oral automatism. Myoclonic seizures are sudden, brief, and similar to the state of shock, which

mostly occur upon waking or during sleeping hours and may be exacerbated by volitional movements as it is referred to as action myoclonus.

Clonic seizures are characterized by repetitive, biphasic, jerky movements, along with repetitive vocalization synchronous with the clonic movement of the chest. They may also be associated with urinary incontinency. Patient with rigid violent muscle contraction and flex limbs in a strained position manifest the symptoms of tonic seizures. Tonic-clonic seizures (formerly known as grand mal) encompass two major parts, including the tonic phase with the sudden, sharp, and tonic contraction of the respiratory muscles, leading to stridor and cyanosis, as well as tongue bite and urinary incontinency. The clonic phase is associated with deep respiration, muscle relaxation, and remaining unconscious. The sudden reduction of muscle tones with the subsequent falling and head drop are among the other features of atonic seizures (14,15).

Continuous seizures are classified as status epilepticus and epilepsia partialis continua. Status epilepticus is a continuous seizure activity with no recovery between the attacks, which is accompanied by tonic-clonic seizures lasting longer than five minutes or two minutes longer than the average seizure duration of the patient. These seizures are considered to be a medical emergency. Epilepsia partialis continua is a rare focal motor seizure, which recurs in seconds or minutes for long durations and is precipitated in the adults with a history of strokes or children with Rasmussen's encephalitis possibly due to chronic viral infections or autoimmune diseases (16).

Epilepsy syndromes could be classified based on whether the associated seizures are partial or generalized and whether the etiology is idiopathic or cryptogenic. The International League against Epilepsy (ILAE) has categorized these syndromes as idiopathic, symptomatic (underlying structural abnormality), cryptogenic, and part of special syndromes (17) (Table 1).

Table 1. ILAE Classification of Epilepsy Syndromes.

Category	Localization-related Syndromes	Generalized Syndromes
Idiopathic	Benign Epilepsy of Childhood with Centrotemporal Spikes (Benign Rolandic Epilepsy) Benign Occipital Epilepsy	Benign Myoclonic Epilepsy in Infancy Childhood Absence Epilepsy Juvenile Absence Epilepsy Juvenile Myoclonic Epilepsy
Symptomatic (underlying structural disease)	Temporal Lobe Frontal Lobe Parietal Lobe Occipital Lobe	Early Myoclonic Encephalopathy Cortical Dysgenesis Metabolic Abnormalities West Syndrome Lennox-Gastaut Syndrome
Cryptogenic	Occurrence of Partial Seizures without Obvious Pathology	Epilepsy with Myoclonic Absences West Syndrome (unidentified pathology) Lennox-Gastaut Syndrome (unidentified pathology)
Special Syndromes	Febrile Convulsions Seizures Occurring Only with Toxic or Metabolic Provoking Factors Neonatal Seizures of any Etiology Acquired Epileptic Aphasia (Landau-Kleffner Syndrome)	

In general, various disorders are classified as epilepsy syndromes in the current literature. Autosomal dominant nocturnal frontal lobe epilepsy is often misdiagnosed with nightmares and has a genetic basis, involving the nicotinic acetylcholine receptors. Rolandic epilepsy or benign centrotemporal lobe epilepsy of childhood is associated with spike discharges over the centrotemporal scalp in the central sulcus (Rolandic sulcus) in electroencephalography (EEG), mostly presenting during drowsiness or light sleep. Benign occipital epilepsy of childhood (BOEC) is characterized by spikes in the occipital regions, which may be associated with autosomal dominant genetic transmission as described by Kuzniecky et al. (18).

Some researchers have classified panayiotopoulos syndrome as a subcategory of BOEC. Patients with childhood absence epilepsy have recurrent absence seizures, generalized spikes (3-Hz), and wave discharges on the EEG. Dravet syndrome (formerly known as severe myoclonic epilepsy of infancy) is variable in individuals, and the onset is mostly accompanied by fever and tonic-clonic patterns.

In the female patients with mental retardation, epilepsy is caused by mutations in the Protocadherin-19 gene. Febrile infection-related epilepsy syndrome and interictal dysphoric disorder are among the less common syndromes of epilepsy. Although they are difficult to be observed in standard EEG, 3-Hz spikes and waves or multiple spikes on the EEG, along with generalized tonic-clonic seizures, may occur in the patients with frontal lobe epilepsy due to the underlying lesion in the frontal area.

Juvenile myoclonic epilepsy may manifest as generalized 4-6 Hz spike waves or multiple spike discharges in the patients with otherwise intact neurological function and normal cognition. On the other hand, 2-Hz slow spike waves on the EEG in these patients, along with developmental delay and mixed generalized seizures, constitute a triad in favor of LGS.

Severe stiffening spasms or unilateral seizures within the first days or weeks of life with poor prognosis have been reported in the patients with Ohtahara syndrome. According to statistics, less than 7% of epileptic patients show seizure activity after specific triggers, such as flashlights, sudden, loud noises, and menstrual cycle (catamenial epilepsy), which are referred to as reflex epilepsy. Unverricht-Lundborg disease, myoclonus epilepsy with ragged red fibers, Lafora disease, neuronal ceroid lipofuscinosis , and sialidosis are a category of disorders that manifest as generalized seizures and progressive dementia and are classified as progressive myoclonic epilepsies.

Ring chromosome 20 syndrome is a distinct epilepsy syndrome with genetic predisposition, which has been described in 30 cases since 1976 (19). Although temporal lobe epilepsy is not a classic syndrome, in most of the cases, the epileptogenic region is observed in the hippocampus, amygdala, and parahippocampal gyrus in the mesial temporal area. Ring chromosome 20 syndrome is considered to be the most prevalent epilepsy syndrome in adults. A triad of developmental delay, infantile spasms, and hypsarrhythmia on the EEG could confirm the diagnosis of West syndrome, the most common cause of which is tuberous sclerosis (20-22).

Medical and Surgical Management: Conventional and Modern Multidisciplinary Approaches

The general treatment of the patients with seizures and epilepsy syndromes is mainly based on the reassurance and education of the patients and their family using information leaflets regarding the support groups for the financial and psychosocial issues of the underlying diseases, along with the avoidance of vigorous physical activities that are critical in the management of these patients.

The specific treatments for seizures are mainly classified into medical therapy with anticonvulsants and surgery. Anticonvulsants are the mainstay of the treatment, and selecting the optimal drugs for the underlying diseases with the least adverse effects is essential in this regard. These medications could be divided into 11 categories based on their action mechanism. Sodium channel blockers (e.g., phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, topiramate, lacosamide, and rufinamide) could enhance the inactivation of sodium channels. GABA-A receptor activators include phenobarbital, benzodiazepines, and clobazam. Felbamate is an NMDA receptor blocker. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor blockers include perampanel and topiramate.

Calcium channel blockers are classified as T-channel blockers and N- and L-calcium blockers, in which ethosuximide and valproate affect the T-channels, while lamotrigine, topiramate, zonisamide, and valproate affect the N- and L-channels. Gabapentin and lamotrigine are H-current modulators, while topiramate and zonisamide inhibit the carbonic anhydrase enzyme. Moreover, ezogabine is a neuronal potassium channel opener (KCNQ [Kv7]). The anticonvulsants that are commonly used for the management of tonic-clonic and partial seizures include carbamazepine, phenytoin, and valproate, while ethosuximide, valproate, and clonazepam are used for the management of absence seizures. Valproate and clonazepam are effective in the management of myoclonic seizures as well. Diazepam and lorazepam are effective in the short-term control of status epilepticus, while the prolonged management is based on the use of phenytoin and phenobarbital. Furthermore, corticosteroids have been reported to positively influence the management of infantile spasms, while physicians should be aware of the increased risk of developing Cushing's disease in these patients (23,24).

In non-pharmacological management, modified Atkins diet and ketogenic diets have shown positive results in the children with epilepsy. Vagal nerve stimulation (VNS) is a palliative technique performed with a stimulating device and has been approved by the Food and Drug Administration (FDA) of the United States for the management of the patients with medically refractory focal-onset epilepsy aged more than 12 years, who are not candidates for curative surgical operations (25). Additionally, the American Academy of Neurology (AAN) has declared that VNS is effective as an adjuvant, long-term treatment option for chronic

or recurrent depression in the patients aged more than 18 years, as well as those with major depressive disorder who are not adequately treated with a minimum of four antidepressants. The AAN guidelines suggest that as an adjuvant treatment of partial or generalized epilepsy, VNS could have positive effects on children, as well as on seizure control in the patients with LGS. In this method, the implantation site should be meticulously monitored for potential infections in children (26). Furthermore, the Neurological Devices panel of FDA has reported that NeuroPace RNS system (an implantable neurostimulator), which is implanted in the cranial fossa, is capable of delivering short trains of the current pulses to interrupt the ictal discharges in epileptic patients, while it is also efficient in performing live EEG recording (27).

Anterior callosotomy was the most common surgical procedure for the palliative treatment of medication-refractory seizures in the patients with atonic seizures. In general, the epileptogenic area of the brain could be identified using live video-EEG monitoring or through the placement of intracranial electrodes. Temporal lobe surgery is considered to be the most successful lobectomy in seizure control (28). In the current literature, there is a study on a patient with unilateral temporal lobe seizure documented by EEG and unilateral hippocampal sclerosis documented by magnetic resonance imaging (MRI), who underwent temporal lobe surgery and was expected to have the class I outcome (i.e., seizure-free or auras only) within two years with the probability of 85%. In addition, the MRI-guided selective laser amygdalohippocampectomy indicated the same positive results as those of the temporal lobe surgery (29). The types of surgical procedures are depicted in Figure 1.

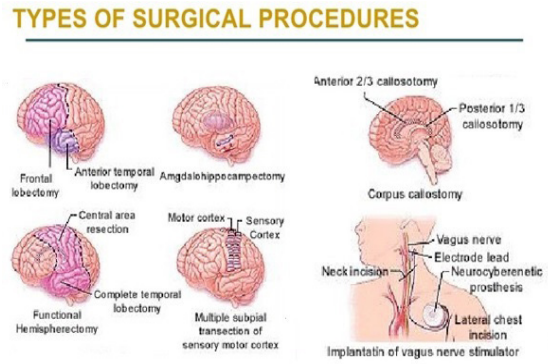

Figure 1. Types of Surgical Procedures for Seizure Surgery.

In a research in this regard, Hyslop et al. described a study involving 25 pediatric patients with MRI-negative partial epilepsy, who underwent focal corticectomy in the 66th Annual Meeting of the American Epilepsy Society (29). The researchers investigated the epileptogenic areas using 3D EEG, single-photon emission computed tomography scanning, and positron emission tomography. According to the findings, %42 of the patients with type I focal cortical dysplasia, %58.3 of the patients with type II focal cortical dysplasia, and %50 of the patients with mild cortical development malformations had a seizure-free status after the operation (30).

Conclusion

According to the results, surgical approaches for medication-refractory seizures are palliative and curative and yield promising results if the epileptogenic area is localized using a multidisciplinary approach via live video-EEG monitoring or direct intracranial electrode placement. Furthermore, the utilization of live modern imaging modalities along with surgical approaches could enhance the success rate of the treatment, while increasing the seizure-free period.

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Conflict of Interest

The authors declare no conflict of interest.

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