

## A REVIEW ON EPILEPSY AND ITS TREATMENT

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### ABSTRACT

An increasing number of infantile epilepsy syndromes have been recognized. However, a significant number of infants (children aged 1-24 months) do not fit in any of the currently used subcategories. This article reviews the clinical presentation, electroencephalographic findings, evolution, and management of the following entities: early infantile epileptic encephalopathy, early myoclonic epilepsy, infantile spasms/West syndrome, severe myoclonic epilepsy of infancy, myoclonic-astatic epilepsy, generalized epilepsy with febrile seizures plus, malignant migrating partial seizures of infancy, hemi convulsions-hemiplegic-epilepsy, benign myoclonic epilepsy, and benign familial/nonfamilial infantile seizures. Issues related to their classification are addressed.

**Keywords:** Febrile, Hemi-convulsions, hemi-plegic, Malignant epilepsy, Infantile spasms.

### INTRODUCTION

Epilepsy is a chronic medical disorder in which a person has repeated seizures (convulsions) over time that affect a variety of mental and physical functions. A seizure is the clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons. Epileptogenesis is the sequence of events that turns a normal neuronal network into a hyper excitable network. Epilepsy may require chronic treatment (with antiepileptic medication and, in some cases, surgery) whereas therapy for an isolated seizure is directed toward the underlying cause and may not require antiepileptic drugs (AEDs). Furthermore, epilepsy often has profound psychosocial ramifications for the patient, and is thus a diagnosis to be assigned with care. Epilepsy and seizures are among the most common neurological conditions affecting all ages. Seizures that occur in patients with cancer may have a variety of causes, including brain parenchymal and meningeal metastasis, the administration of cytotoxic chemotherapy and toxic-metabolic encephalopathy.

### DEFINITION

**Epilepsy**, any of a group of syndromes characterized by paroxysmal transient disturbances of brain function that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, psychic or sensory disturbances, or perturbation of the autonomic nervous system; symptoms are due to disturbance of the electrical activity of the brain.

### Types of Epileptic Seizures

#### PARTIAL

Simple partial seizures cause motor, sensory, autonomic, or psychic symptoms without an obvious alteration in consciousness. These seizures may also be manifested as changes in somatic sensation (e.g., paresthesias or tingling), vision, equilibrium, autonomic function olfactory changes, and hearing.

Complex partial seizures are characterized by focal seizure activity, accompanied by transient impairment of the patient's ability to maintain normal contact with the environment. Partial seizures can spread to involve both cerebral hemispheres and may produce a generalized

seizure, usually of tonic-clonic variety. Secondary generalization is often observed following simple partial seizures, especially those with a focus in the frontal lobe.<sup>5</sup>

### GENERALIZED

Generalized seizures arise from both cerebral hemispheres simultaneously.<sup>5</sup> Absence seizures (petit mal) are characterized by sudden, brief lapses of consciousness without loss of postural control. The seizure typically lasts for only seconds; consciousness returns as suddenly as it was lost, and there is no postictal confusion. Atypical absence seizures have features that deviate clinically and electro physiologically from typical absence seizures. A simple absence seizure is defined as a brief clouding of the sensorium, or loss of consciousness, accompanied by certain generalized epileptic discharges without other detectable clinical signs. A complex absence seizure indicates that other signs are also present. Generalized, tonic-clonic seizures (formerly grand mal) are the main seizure type in approximately 20% of all persons with epilepsy. Atonic seizures are characterized by sudden loss of postural muscle tone lasting 1 to 2 seconds. Consciousness is briefly impaired, but there is usually no postictal confusion.<sup>5</sup> Myoclonus is a sudden and brief muscle contraction that may involve one part of the body or the entire body.

### UNCLASSIFIED

Not all seizure types are partial or generalized; this appears to be true of seizures that occur in neonates and infants.<sup>5</sup> Some of the seizures that occur in neonates and infants likely result, in part, from differences in neuronal function and connectivity in the immature brain.

### ETIOLOGY

The neurotransmitters mediating the main part of synaptic transmission in mammalian brain are amino acids; gamma amino butyric acid (GABA) and glutamate are the principal inhibitory and excitatory neurotransmitters, respectively. GABA is the major inhibitory amino acid neurotransmitter in the mammalian CNS. Its receptors have been divided into two main types: GABA<sub>A</sub> (the more prominent subtype) is a ligand-gated Cl<sup>-</sup> ion channel that is opened after the release of GABA from presynaptic neurons. The GABA<sub>A</sub> receptor protein has been well characterized by its high abundance and its role in almost every neuronal circuit. GABA<sub>B</sub>, a member of the G-protein coupled receptor family, is linked

both to biochemical pathways and to regulation of the ion channels.<sup>11</sup> Most primary epilepsies have a genetic basis. As in many other idiopathic diseases such as diabetes, the mode of inheritance is complex.

### PATHOPHYSIOLOGY OF EPILEPSY

It is necessary to differentiate epilepsy, which is a progressive neurologic disorder of the brain, from seizures themselves, which are distinct, transient occurrences caused by abnormal, excessive, or synchronous neuronal activity in the brain.<sup>9</sup> Signs and symptoms of seizures may include warnings, such as visual or sensory auras, déjà vu, tingling fingers, altered awareness, and abnormal or convulsive movements. The pathophysiology underlying the epileptic process includes mechanisms involved in initiation of seizures (ictogenesis), as well as those involved in transforming the normal brain into a seizure-prone brain (Epileptogenesis).

### MECHANISMS OF ICTOGENESIS

Hyper excitation is the key factor underlying ictogenesis (Figure 6). Excessive excitation may originate from individual neurons, the neuronal environment, or neuronal networks. Excitability arising from the neuronal environment may result from both physiologic and structural changes. Physiologic changes include alterations in concentrations of ions, metabolic alterations, and in neurotransmitter levels. Structural changes affect both neurons and glia. Consequently, glial K<sup>+</sup> buffering may be affected and may lead to epileptic activity.<sup>3,11</sup> Extracellular Ca<sup>2+</sup> concentration decreases by over 85% during a seizure, preceding the changes in K<sup>+</sup> concentration by milliseconds. However, Ca<sup>2+</sup> levels return to normal faster than K<sup>+</sup> level

### MECHANISMS OF ICTAL-INTERICTAL TRANSITION AND EPILEPTOGENESIS

Both nonsynaptic and synaptic mechanisms that affect synchronicity, signal amplification, and spread of seizures play a role during ictal-interictal transition, promoting Epileptogenesis

### NONSYNAPTIC MECHANISMS

Failure of Na<sup>+</sup>-K<sup>+</sup> pumps due to hypoxia or ischemia is known to promote Epileptogenesis in animal models, and interference with Cl<sup>-</sup>-K<sup>+</sup> transport, which controls intracellular Cl<sup>-</sup> and regulates GABA-activated inhibitory Cl<sup>-</sup> currents, may lead to enhanced excitation. Excitability of synaptic terminals

depends on the extent of depolarization and the amount of neurotransmitter released. Synchronization following abnormal bursts of spikes in the axonal branching of thalamocortical relay cells plays a key role in Epileptogenesis.

### SYNAPTIC MECHANISMS

Synaptic pathophysiology of epilepsy and epileptic disorders primarily involves reduced GABAergic inhibition or enhanced glutamatergic excitation.

### GABA

GABA levels have been shown to be reduced in the cerebrospinal fluid (CSF) of patients with certain kinds of epilepsy, such as infantile spasms and untreated generalized tonic-clonic seizures, and in excised epileptic tissue from patients with drug-resistant epilepsy, suggesting that these patients have decreased inhibition.

### GLUTAMATE

Hippocampus recordings from conscious human brains have shown sustained increases in the levels of extracellular glutamate levels during and preceding seizures. GABA levels remain low in the epileptogenic hippocampus, but during seizures, GABA concentrations increase, although mostly in the non-epileptogenic

Hippocampus. This leads to a toxic increase in extracellular glutamate due to reduced inhibition in the epileptogenic areas

### ROLE OF GLIAL CELLS IN EXCITATION

Although most of the work on the pathogenesis of epilepsy has focused on neurons, glial cells are known to play a key role in buffering functions that maintain the uptake of K<sup>+</sup> and glutamate; disrupting these functions may cause hyper excitability. Recent evidence also suggests that glutamate release from glia can generate a paroxysmal depolarizing shift (PDS), the prolonged depolarization reflected in EEG recordings of interictal discharges. Even in the absence of synaptic interactions, astrocytic release of glutamate can trigger PDS-like events.

### DIAGNOSIS

The examination of infants and children is of greater value, because the presence of dysmorphic and cutaneous abnormalities allows for the diagnosis of a number of highly characteristic cerebral diseases that give rise to epilepsy. Several laboratory studies are usually included in the initial diagnostic evaluation, such as a complete blood count, blood chemistry profiles, liver and

thyroid function tests, an EEG, and a brain study, preferably with magnetic resonance imaging (MRI). Computed tomography (CT) scanning may be the only practical study in an emergency or for very young children.<sup>12</sup> Some patients may later require video/EEG or prolonged EEG monitoring, either in the hospital or with portable equipment in the home.

Cardiac stress tests, Halter monitoring, tilt-table testing, long-term patient activated cardiac monitors, and sleep studies may also be performed. A second battery of diagnostic tools includes another EEG to record brain waves. Electrical signals from brain cells are recorded during or between seizures and may show special patterns to determine whether the person has epilepsy. CT or MRI scans may be used to search for any growths, scars, or other physical conditions in the brain that might be causing seizures. In a few research centers, positron emission tomography (PET) is used to identify areas of the brain that are producing seizures.

### Causes of Epilepsy

There is a clear cause for epilepsy in only a minority of the cases. Typically, the known causes of seizure involve some injury to the brain. Some of the main causes of epilepsy include:

1. low oxygen during birth
2. head injuries that occur during birth or from accidents during youth or adulthood
3. brain tumors
4. genetic conditions that result in brain injury, such as tuberous sclerosis
5. infections such as meningitis or encephalitis
6. stroke or any other type of damage to the brain

### SYMPTOMS

- Sudden falls
- Involuntary jerky movements of limbs whilst awake
- Blank spells
- Unexplained incontinence of urine with loss of awareness, or in sleep
- Odd events occurring in sleep, e.g. fall from bed, jerky movements, automatisms
- Episodes of confused behavior with impaired awareness
- Possible simple partial seizures
- Epigastria fullness sensation
- Premonition
- Elation, depression

- De-personalisation, derealisation
- Inability to understand or express language (written or spoken)
- Loss of memory, disorientation
- Olfactory, gustatory, visual, auditory hallucinations
- Focal motor or somatosensory deficit, or positive symptoms(jerking, tingling)

### TREATMENT OF EPILEPSY

Zonegran is indicated for use as an adjunctive therapy for treatment of partial seizures (or *focal seizures*) in adults with epilepsy.

### MECHANISM OF ACTION

The precise mechanism(s) by which zonisamide exerts its antiseizure effect is unknown. In animals, zonisamide was effective against tonic extension seizures induced by maximal electroshock but ineffective against clonic seizures induced by subcutaneous pentylenetetrazol. The relevance of these models to human epilepsy is unknown. Zonisamide may produce these effects through action at sodium and calcium channels. *In vitro* pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type  $Ca^{2+}$  currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. *In vitro* binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion which does not produce changes in chloride flux. Other *in vitro* studies have demonstrated that zonisamide (10-30  $\mu\text{g}/\text{mL}$ ) suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. *In vivo* microdialysis studies demonstrated that zonisamide facilitates both dopaminergic and serotonergic neurotransmission. Zonisamide also has weak carbonic anhydrase inhibiting activity, but this pharmacologic effect is not thought to be a major contributing factor in the antiseizure activity of zonisamide.

### Side Effects

Common side effects of Zonegran include but are not limited to:

1. Renal calculi
2. Drowsiness
3. Ataxia
4. Loss of appetite

### 5. Gastrointestinal symptoms

Possible rare but serious side effects of Zonegran include but are not limited to:

1. Severe rash (i.e. Stevens Johnson Syndrome [SJS] and toxic epidermal necrolysis [TEN])
2. Serious hematologic events, such as aplastic anemia or agranulocytosis

### Pregabalin: a new drug for epilepsy, neuropathic pain and anxiety

Pregabalin (PGB) is the latest compound that joins the list of approved "new" AEDs. In addition to epilepsy, it has demonstrated efficacy for the treatment of neuropathic pain and generalised anxiety disorder.

### Mechanism of Action

PGB [(S)-3-(aminomethyl)-5-methylhexanoic acid] (Figure) is licensed under the trade name Lyrica R. Similar to its predecessor gabapentin but with greater Potency, PGB binds to the alpha-2-delta subunit site of neuronal voltage-gated calcium channel, resulting in reduced depolarization-induced calcium influx at nerve terminals with a consequential reduction in the release of excitatory neurotransmitters.

### Pharmacokinetics

PGB has a favorable pharmacokinetic profile it is rapidly and extensively absorbed after oral dosing in the fasted state. Administration of PGB with food has no clinically relevant effect on the amount of PGB absorbed although the rate of absorption may be decreased. Maximal plasma concentration is reached 1 hour after single or multiple doses and steady state is achieved within 24 to 48 hours after repeated administration. The oral availability of PGB is high at >90% and is independent of dose. The maximal plasma PGB concentration and total exposures are proportional to dose after multiple dosing. Routine monitoring of plasma concentrations of PGB is not necessary. The mean elimination half-life of PGB is 6.3 hour. PGB undergoes negligible metabolism in humans and is Excreted virtually unchanged by the kidneys. Because of this, dose reduction in patients with impaired renal function is needed. PGB does not bind to plasma Proteins. It is not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the cytochrome P450 system. Consequently, PGB has very low potential for pharmacokinetic drug-drug

interactions, which is a particular advantage for its use

### Safety and Tolerability

PGB is generally well tolerated the most common adverse reactions were dizziness (28.9% vs. 8.9% for placebo) and somnolence (23.7% vs. 8.8% for placebo). Other notable central nervous system side effects include par aesthesia and ataxia. Non-CNS side effects considered common include peripheral edema and weight gain, although they rarely (<1%) directly led to discontinuation of PGB.

### Recent studies

Eslicarbazepine, brand name Zebenix®, a new epilepsy drug, was approved for sale in Europe. This drug, discovered in 1996, is chemically related to carbamazepine (Tegretol™) and oxcarbazepine (Trileptal™), but it may have fewer drug interactions than do carbamazepine and oxcarbazepine. Researchers in Sweden and Portugal reported results of a randomized controlled trial in 393 patients given either 0 (placebo), 400, 800 or 1200 mg of drug in a convenient single daily dose. Seizures were reduced by an average of 33% with the 800 and

1200 mg dose, significantly better than placebo. About 20-25% of the patients in the higher dosage groups discontinued treatment because of side effects, most commonly dizziness, sleepiness or headache. A second trial, performed in Poland, Hungary, Germany and Portugal enrolled about 400 patients, and found similar outcomes, with a 43% median seizure reduction rate at doses of 1200 mg per day. A third favorable trial brought the total of patients studied to 1049. The European authorities approved the medication as add-on treatment for adults with partial-onset seizures, with or without secondary generalization.

### CONCLUSION

seizures are common and the majority of children who experience them do well. Most outgrow the tendency to have seizures and the seizures do not cause lasting intellectual or neurologic damage. Very few children with a very high risk of recurrence need to be exposed to anticonvulsant therapy. In such cases, treatment decisions have to be made by the physician and the family after weighing the-morbidity of recurrences versus therapy, and have to be ultimately made on an individual basis.

**List of Anti epileptic drugs**

Type	First choice	Second choice	Alternatively
Simple partial	Carbamazepine phenytoin	Valproate	Lamotrigine,gabapentin
Complex partial	Phenytoin, carbamazepine	Lamotrigine,gabapentin	Clobazam, zonisamide
Absence	valproate	Ethosuximide	Clonazepam
Myoclonic	Valproate	Topiramate	Clonazepam
Atonic	Valproate	Clobazam, clonazepam	Lamotrigine
Febrile	Diazepam	—	—
Status	Lorazepam	Fosphenytoin	Anaesthetics

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