An Outlook to Non-Pharmacological and Novel Approaches to Combat the Uncurable Firing Disorder

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ABSTRACT

Epilepsy, a serious neurological abnormality which exhibit neuronal misfiring and send out of incorrect signals as its major characters which ultimately lead to seizures. The etiological factors of seizures vary widely ranging from Hypoxia to brain tissues, infection or injury to brain tissues and also certain inborn defects, stress, consumption of illicit drugs, withdrawal of alcohol and the current therapy cannot completely cure epilepsy. Drug resistant epilepsy (also known as pharmaco resistant epilepsy) is a chronic, life threatening condition that affect the quality of life and ultimately lead to death of the patient. The concentration related peripheral side effects of antiepileptic medications remains a major challenge to the researchers. Prevention of epilepsy can be done in 60% of the cases by the use of AEDs but the Non-conventional therapy helps in symptomatic relief and seizure frequency reduction especially in case of refractory or drug resistant epilepsy. These treatments also play a role in preventing the toxicity problems of AEDs. This review mainly deals with the innovative strategies for the site specific therapeutic maintenance of drug in the epileptic foci and several methods to diagnose epilepsy.

Keywords: Seizures, epilepsy, adverse effects, Seizure foci, Therapeutic concentration.

INTRODUCTION

Epilepsy is a disorder exhibited by neuron with repetitive seizures affecting central nervous system, unprovoked by a neurologic insult. The prevalence of epilepsy is nearly one lakh per year and it is 0.5-1% (5x higher in developing countries) Fig 1.

Seizure disorder is also known as Epilepsy. The seizure is said to be a hyper excitability of a group of cortical abnormal neurons. Seizure is a electrical activity of brain which is a sudden surge which immensely affect the individuals behavioural and cognitive aspects.

Based on the area and number of lobes affected the seizure type also varies.¹ Epileptogenesis is a cascade of events that slowly transform normal neuronal network to over excitable one.

The factors that affect the pathophysiology of epilepsy can be broadly categorized to intrinsic and extrinsic.

The onset of symptoms can occur at any age group in any point if their life period. Epidemiological studies suggest that it ranks fourth position among the neurological diseases.

Females and children of age less than 4 months are more vulnerable to seizure attack than men. Symptoms of epilepsy get worsened beyond the mid 50s and get milder until about the age 10.

The risk factors and seizure trigger of epilepsy vary widely.

This should be carefully monitored as it requires immediate medical requisites.

Pathophysiology of epilepsy is very complex and it involves various underlying intrinsic and extrinsic mechanisms which was an eye opener to the discovery of AEDs. But now, there is evolution of dreadful pharmaco resistant epilepsy which is a serious concern.

There urging need to counteract this by using non pharmacological treatment and non conventional therapy is increasing day to day.²⁵

Symptoms

* Confused stage
* Rapid blinking of eyelids
* Repetitive and rapid jerking movements
* Unconsciousness or unawareness
* Psychological problems

Immediate Medical Help Requisites

Difficulty in rousing at varying intervals

* Headache
* Pupillary constriction and dialation
* Blurred vision
* Nausea
* Pregnancy condition
* Patients with varying glucose level
* Head injury²⁵
Risk Factors and Seizure Triggers (Fig 2 & Table 1)

Table 1: Risk Factor and Seizure Triggers

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Seizure Triggers</th>
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<tbody>
<tr>
<td>• Small Babies with less body weight</td>
<td>• Skipping medicines</td>
</tr>
<tr>
<td>• Babies with seizures in the early stage</td>
<td>• Insomnia</td>
</tr>
<tr>
<td>• Babies with brain abnormalities</td>
<td>• Sickness</td>
</tr>
<tr>
<td>• Cerebral haemorrhage</td>
<td>• Stress/strain</td>
</tr>
<tr>
<td>• Impaired vascularisation in brain</td>
<td>• Chronic alcoholism or as a consequence of withdrawal syndromes</td>
</tr>
<tr>
<td>• CNS trauma/hypoxia</td>
<td>• Mood elevating drugs</td>
</tr>
<tr>
<td>• Lesions in brain</td>
<td>• Any drug that antagonize the action of AED</td>
</tr>
<tr>
<td>• Brain Infections</td>
<td>• Mal nutrition</td>
</tr>
<tr>
<td>• Stroke</td>
<td>• Improper food habits</td>
</tr>
<tr>
<td>• Genetical reasons</td>
<td>• Hormonal imbalance</td>
</tr>
<tr>
<td>• Functional disabilities</td>
<td>• Photophobia</td>
</tr>
<tr>
<td>• Convulsion after severe head injury</td>
<td>• Specificity</td>
</tr>
<tr>
<td>• Past historical background Neuro degeneration in late stage of epilepsy</td>
<td></td>
</tr>
<tr>
<td>• Neuronal imbalance</td>
<td></td>
</tr>
<tr>
<td>• infantile spasm</td>
<td></td>
</tr>
<tr>
<td>• Long episodes of seizures lasts for more than 30 mts</td>
<td></td>
</tr>
<tr>
<td>• Narcotic drugs</td>
<td></td>
</tr>
<tr>
<td>• Mild head injuries/unknown cause</td>
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</tbody>
</table>

Table 2: Factors Leading to Epilepsy

<table>
<thead>
<tr>
<th>Intrinsic Factors</th>
<th>Extrinsic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The type, number and distribution of voltage gated channels</td>
<td>• Variation in concentration of extracellular ion.</td>
</tr>
<tr>
<td>• By Receptor chemical modification</td>
<td>• Remodeling of synaptic traffic signals.</td>
</tr>
<tr>
<td>• Second-messenger systems activation - Binding of norepinephrine to its alpha receptor.</td>
<td>• Transmitter metabolism modulators.</td>
</tr>
<tr>
<td>• Modulating gene expression, as by RNA editing</td>
<td></td>
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</tbody>
</table>

Table 3: Dietary Factors

<table>
<thead>
<tr>
<th>Dietary or Metabolic Factors</th>
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<tbody>
<tr>
<td>Reduction in blood glucose or blood insulin</td>
</tr>
<tr>
<td>Hypersensitivity reaction to various food items</td>
</tr>
<tr>
<td>Reaction to monosodium glutamate</td>
</tr>
<tr>
<td>Ketogenic diet</td>
</tr>
<tr>
<td>Atkins diet</td>
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</tbody>
</table>

Table 4: Non Pharmacological Treatments

<table>
<thead>
<tr>
<th>Lifestyle changes</th>
<th>Psychological approach</th>
<th>Promotion of emotional well being</th>
<th>Physical therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Exercise</td>
<td>• Avoidance</td>
<td>• Yoga</td>
<td>• Acupuncture</td>
</tr>
<tr>
<td>• Sleep hygiene</td>
<td>• Relaxation techniques</td>
<td>• Reduction in psychiatric co-morbidity</td>
<td></td>
</tr>
<tr>
<td>• Alcohol</td>
<td>• Biofeedback</td>
<td>• Meditation</td>
<td></td>
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</tbody>
</table>
Table 5: Various Routes for Delivery of Anti-Epileptic Medications

<table>
<thead>
<tr>
<th>Routes</th>
<th>Possible methods for direct delivery of AEDs to brain</th>
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<tbody>
<tr>
<td>Rectal</td>
<td>• CSF delivery</td>
</tr>
<tr>
<td>Skin</td>
<td>• Drug wafers</td>
</tr>
<tr>
<td>Nasal / Buccal</td>
<td>• Local perfusion</td>
</tr>
<tr>
<td>Inhaled</td>
<td>• Seizure-activated drugs</td>
</tr>
<tr>
<td>Direct delivery to CNS</td>
<td>• Liposome-microsomes</td>
</tr>
<tr>
<td></td>
<td>• Cell transplants</td>
</tr>
<tr>
<td></td>
<td>• Gene therapy</td>
</tr>
</tbody>
</table>

Mechanisms of Seizure Origin at Cellular Level

Experimental Models of Seizures and Epilepsy

Using Animal Models
- MES (maximal electroshock) induced model
- Pentylenetetrazole (PTZ) model
- Amygdala kindling model
- Post-status epilepticus model
- Threshold model
- Implant model
- Hydralazine induced model

Pharmacor Resistant Epilepsy

Characteristic epilepsy to which drugs are resistant. This is a chronic condition and treatment options are rare. Accounts a major portion of mortality due to epilepsy. Side effect of ARDs can be considered at this context, because increment in dosage to attain cure may have a large impact on patient’s quality of life (Fig 3).

Pathophysiology of Epilepsy

Epileptic seizures generally arise because of hyper synchronous membrane excitability. Pathophysiological mechanisms of some forms of epilepsy are partially understood.

Some proposals:
- Excitatory glutamatergic synapses
- Excitatory amino acid neurotransmitter (glutamate, aspartate)
- Abnormal tissues — tumor, AVM, dead area
- Genetic factors (20%)

Figure 1: Causes of Epilepsy

Figure 2: Risk Factors

Figure 3: Side Effects of Antiepileptic Drugs

Treatment Options

Non-medicated Therapy

Herbal Medicine and Homeopathy
- Less side effects
- Treat the underlying and thereby the symptoms
Homeopathy
Here the active ingredient present in trace quantities are given after a series of dilutions.  

Dietary Therapies
Ketogenic Diet
Due to the calorie restrictions followed in this diet, nutritional deficiencies may occur. Fluid restrictions are also there. All these insists the mandatory supplementation with iron, calcium etc.  

Atkins Diet
The amount of carbohydrates in the diet were limited to10g/day. There the body utilize fat as the main source of energy. Since fat is considered as the fuel this is highly useful to obese individuals to control the body weight effectively. The success of the diet also lies in higher protein content, and its access to fluid or calorie usage. Further more the fasting is not mandatory at the beginning of the diet. Due to all these differences, it is applicable even to children.  

Oligoantigenic Diet
It consist of variety of food but in small quantities. The diet is quite expensive and maintenance is difficult. Failure occur due food allergies. Cause significant reduction in seizures.  

Vitamins in Epilepsy
Main role:
- Helps to prevent side effects of AEDs
- Improvement in EEG
- Seizure frequency reduction
- Symptomatic relief
- Neurotransmitter resetting  

Vitamin E
Tocopherol can correct the neurological imbalance of cortical neurotransmitters through its positive mediation by limiting the spread of uncontrolled neurological discharge.  

Thiamine
This can be used to manage epilepsy that develops during the late stage of the life time. Long term diet devoid of Thiamine may lead to seizures in chronic drinkers and also in alcoholic non users with epilepsy; these seizures can be managed with supplementation of vitamin B1.  

Pyridoxine (vitamin B6)
Vitamin B6 is very important to maintain the glutamate level in the brain. In the case B6 deficiency, chance of various developmental and mental disorders are high. It is one of the important add on therapy to control seizure. Pyridoxine mediated epilepsy is an autosomal recessive disease associated with refractory seizures in the early life stages. The symptomatic relief is possible with excessive dosage of pyridoxine but if no proper treatments given immediately non recoverable injury to neuron may happen.  

By intravenous administration of B6 diagnostic aspects are fulfilled, leads to termination of seizure with very short duration of time.  

Pyridoxal Phosphate
Mainly used to treat refractory epilepsy in children with unknown cause. Seizure can be of either generalized or partial form, symptomatic relief is possible with in 24 hours. It also plays a significant role in controlling the most dangerous absence seizures. EEG findings are a major substantiating evidence.  

Vitamin D
With drugs such as phenytoin and phenobarbitone rate of production of liver enzymes that metabolize vitamin D which lead to Rickets and Osteomalacia. This can be controlled by vitamin D supplementation.  

Folic Acid
Infants are mostly prone to seizures triggered by folate deficiencies, which leads to life threatening syndromes and certain psychological issues. The main focus of treatment is to develop a corrective therapy for the defective mechanism of transport of folic acid. This disorder is due to impaired folate transport across the BBB into the brain. The folic acid is administered in its active form to counteract the problems related to transport mechanism.  

Biotin
It usually has drug interaction with anti epileptic drugs like phenytoin, carbamazepine and Phenobarbital and some drugs reduce its GI absorption. Consequences of Biotin deficiency leads to excessive oxidation of unsaturated fatty acids, catabolism of proteins and glucose production from non carbohydrate sources. Medical interventions can be applied to correct this disorder. It mainly affects children below 6 years of age.  

Other Supplements
Omega-3 Fatty Acids
Engaged in seizure reduction. But the role of essential fatty acids with variable pharmacological results were shown in some studies.  

Magnesium
Magnesium has good anticonvulsant action when given intravenously in experimental animals like dog, cat, rats etc. Magnesium plays a major role in seizure frequency reduction. Severity of grandmal seizure is enhanced by decreased level of magnesium in plasma and cerebro spinal fluid. Oral route of magnesium administration proves a positive response in some EEG results.
Manganese
In patients with trauma as a cause for epilepsy, manganese level in blood is higher. The development of seizure and deficiency is not categorised under malnutrition. The deficiency of manganese is a major contributing factor. Presence of manganese in the diet may prevent seizure induced as a result of hydralasine. Several studies shows that the deficiency of mineral manganese increases the chance to seizure induced by electric shock. There is no relation with frequency of convulsion and the concentration of manganese in the body after AED therapy.

Taurine
Used in patients with chronic refractory epilepsy. It modulates membrane excitability by suppressing calcium and other neurotransmitter release. It diminishes the release of mineral calcium from the mitochondria. Dose is 200 mg - 21 g per day. Some results showed remarkable decrease of frequency attack in case of epilepsy.

Dimethylglycine
Seizure frequency reduction is its major role. Dimethylglycine deficiency cause marked increase in seizures.

Epilepsy Surgery
Epilepsy surgery is an acceptable methods for controlling seizure attack and proved beneficial to the victims with pharmacoresistant epilepsy.

Three main principles of epilepsy surgery:
• Incision of epileptic foci
• Interruption of seizure propagation nerve pathways.
• Introduction of implantation device.

Other Surgical Options
• Responsive neuro stimulation device (RNS)
• Lobe resection – high efficacy
• Multiple subpial transaction (MST)
• Corpus callosumotomy
• Hemispherectomy
• Lesionectomy

Vagus Nerve Stimulation
Drug resistant partial seizures are commonly treated using VNS. It is generally used as an adjuvant therapy in children more than 12 years and also in adults.

It is a subcutaneously implanted device. Serious adverse events are rare. In situations where intracranial surgery is not applicable, VNS is considered.

Cortical Stimulation
The main principle is direct stimulation of cerebral cortex by applying electrocardiography technique. Useful for patients refractory focal and bi temporal lobe epilepsy. Applicable when surgery is not possible. Shows marked reduction in seizure frequency and intensity.

Brain Neuronal Stimulation Strategies

Deep Neuronal Stimulation to Brain
Symptomatic control of seizures preferably tremors is achieved by this surgery which focus only on damaged nerve cells. Measures of seizure severity and quality of life also improved over time.

Trans cranial Magnetic Stimulation
This could reduce frequency of seizures by suppressing excitability of cortex.

Trigeminal Nerve Stimulation
Low frequency (120 Hz) electrical signal is applied to innervations of trigeminal nerve externally. TNS possess external electrodes with an external pulse generator. Mood elevation and reduction in seizure frequency is observed in patients with pharmaco resistant epilepsy.

Non Pharmacological Treatment of Epilepsy

Rare Treatment Options for Epilepsy

Aroma combination therapies are usually recommended and the duration of treatment is usually more than 12 months.

Alerting Seizure using Dogs
It is one among the recent advances which mainly focuses on the seizure frequency reduction in patients suffering from pharmaco resistant epilepsy.

Statistical data support this statement. But no RCTs are available to prove this.

AED Delivery Routes

Diagnosis

Strategy
• Taking history directly through patient
• Medical support
• Hospital data system

History
✓ Event
✓ Previous medical history
✓ Drug and immunization history
✓ History from family and society

CONCLUSION
Our nervous system is very complex and seizures may occur due to any problem related to it. When a normal nervous system cannot fulfil its nutritional requirements,
it can result in epilepsy. The causes of epilepsy can be unknown or in conjunction with a specific disease.

The management of toxicity problems of AEDs and pharmacoresistant epilepsy can be done by non pharmacological approaches and nonconventional AEDs. The success of psychological approaches where western medicines fail is considered as strong evidence.

To treat chronic conditions, complementary medicines are attributable nowadays. The prevention of epilepsy is done by hormonal therapies, modifications in diet and also by treating nutritional deficiencies of CNS.

Diagnostic evaluation is also important and diagnostic technologies are really worthwhile.

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