Epilepsy: Neurological Disorder—a Review

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Abstract: Epilepsy is a complex chronic disease experienced by millions and a cause of considerable mortality worldwide. Seizures, epileptogenesis and the state of recurrent unprovoked seizures define epilepsy itself. Although it is defined by the occurrence of spontaneous epileptic seizures, many research studies indicate that this disorder is linked to behavioral, psychiatric and cognitive disorders as well as to sudden death. This review summarizes the knowledge related to epilepsy disorder and the mechanisms behind.

Keywords: Epilepsy, epileptogenesis, ion channels, seizures

INTRODUCTION

Epilepsy is a chronic neurological disorder and one of the oldest conditions known to mankind which is characterized by spontaneous recurring seizures. According to estimation, 50 million individuals have a diagnosis of epilepsy worldwide. Many studies report a higher incidence in males than females (Hauser et al., 1993). According to Donner and Snead (2006), the incidence of epilepsy is highest for children below five years of age and the elderly. “Mortality is increased in patients with epilepsy and increased mortality risk in childhood-onset mortality is primarily seen in patients with neurologic abnormalities or intractable epilepsy (Shinnar and Pellock, 2002).”

A person with epilepsy may periodically experience epileptic seizures. The common types of epilepsy include petit mal, psychomotor epilepsy and grand mal. Petit mal occurs almost exclusively in children. Children experiencing a petit mal seizure lose contact with reality for 5 to 30 sec but do not lose consciousness or display convulsions (Van De Graff, 2000). Psychomotor epilepsy involves involuntary lip smacking or hand clapping. In addition, if motor areas in the brain are not stimulated, a person with psychomotor epilepsy may wander aimlessly until the seizure subsides. A serious form of epilepsy, grand mal seizure, is characterized by periodic convulsive seizures that render a person unconscious (Van De Graff, 2000).

Seizures:
Seizure is sudden event of abnormal, synchronous excitation of a neuronal population which is confined to the abnormal region or spreading throughout the brain and typically last seconds or minutes but can be prolonged and continuous in the case of status epilepticus. It is becoming more obvious from research that an epileptic region of the brain consists of many small hyper excitable networks. Variety of electro physiologic changes occurs frequently in epileptic regions that move the brain into different seizure probability states. These abnormal events may include micro seizures, or seizure like electro physiologic events, clinical seizures may result when these micro seizures slowly enlarge, begin to unite and engage more and more of the normal brain in surrounding regions.

Now question arises what is the mechanism behind development of these seizures. Most likely mechanism is that some of the principal cells in an excitatory center of the epileptic region tend to fire in abnormal high frequency bursts, which are likely due to enhanced recurrent excitatory connections. Due to aggressive firing of the excitatory neurons, excitatory synapses are occur, but there treatment, Clinical presentation and prognosis are widely different.

The purpose of the review is to study the pathophysiology of epilepsy on genetic/molecular base that such types of genes are prone to epilepsy.

Patients with childhood onset epilepsy have symptoms of depression, sleep disturbances and pain syndromes, impaired intellectual function consistent with mental retardation (Berg, 2011; Camfield et al., 2002).

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facilitated with repetitive stimulation, producing stronger activation of recurrent excitatory circuits. Simultaneously, producing a decline in synaptic strength as a result of which seizure activity is produced. According to another research, these seizures do not start abruptly but may develop with a series of changes in electrical activity of the brain.

In Epilepsy, seizures result from paroxysmal, uncontrolled discharges of electricity from the brain that arise predominantly from the cerebral cortex. According to estimation, 25 to 40% of intractable or medication-resistant childhood epilepsy is attributable to MCDs and at least 75% of patients with MCDs will have epilepsy.

Epilepsy types:

Benign familial neonatal convulsions: BFNC is a rare form of idiopathic generalized epilepsy inherited in an autosomal dominant manner. Convulsions occur in the neonatal period in this syndrome.

Generalized Epilepsy with Febrile Seizures plus (GEFS+): It is a familial epilepsy syndrome in which febrile seizures occur between ages of 6 months and 6 years. It also exhibit autosomal dominant inheritance. Febrile seizures are the most common convulsive event in humans affecting 2 to 5% of children (Baulac et al., 2008).

Severe myoclonic epilepsy of infancy: Severe myoclonic epilepsy of infancy is a rare convulsive disorder prevailed by febrile seizures which occur during the first year of life followed by impaired psychomotor development and ataxia but the seizures in this disorder are usually unresponsive to anticonvulsant drugs.

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE): In Patients affected with ADNFLE, partial seizures occur during sleep and are originate in the frontal cortex. Most of the ADNFLE cases are milder and shows a positive response to carbamazepine treatment (Saenz et al., 1999).

Refractory (intractable) epilepsy: This type of epilepsy is established due to inadequate seizure control despite using potentially effective anti-epileptic drugs (Beleza, 2009). Patients with refractory epilepsy show increased risk of psychiatric, psychosocial and medical problems. According to various studies, onset of early intractable seizures causes an increased risk for intellectual functioning and adaptive abilities impairment (Saneto and Wyllie, 2000). One of the treatment forms for refractory epilepsy is a Resective surgery, based on the removal of the entire epileptogenic area without causing permanent neurological deficit (Beleza, 2009).

Malformations of Cortical Development (MCD) and epilepsy: There exists a high clinical association between MCD and epilepsy in infants, children and adults (Hannan et al., 1999; Schwartzkroin and Walsh, 2000; Pillai et al., 2002) and it is estimated that almost 20% of all epilepsies are caused by MCD (Crino et al., 2002).

Epilepsy results from the Malformations of Cortical Development (MCD) which result from abnormalities altering the normal processes of cortical development. It involves dysfunction of the cells that play key roles in formation of cerebral cortex under normal circumstances (Schwartzkroin and Walsh, 2000; Hua and Crino, 2003; Hader et al., 2004; Wong, 2007).

MCD involves a wide range of structural changes which results from changes at various stages such as: proliferation, migration, differentiation and apoptosis in precursor neuronal or neuronal cells during cortical development (Becker and Bonni, 2004).

The molecular mechanisms underlying the formation of MCD are still largely unknown and the treatments for epilepsy due to MCD are often ineffective or limited (Wong, 2007). MCD-related epilepsy may be resistant to AEDs and may require resection. Therefore, MCD formation and the occurrence of epileptic seizures in children is a great public health concern.

Hormonal aspects of epilepsy: Different hormonal profile alterations have been described for epilepsy patients. The human brain directly regulates hormonal status through hypothalamus-pituitary-endocrine gland feedback loops. Epilepsy and the medications used to treat epilepsy can have direct effects on regulation of these hormone systems.

Epilepsy and AEDs can affect hormone levels, including the limbic system, hypothalamus, pituitary, peripheral endocrine glands, liver and adipose tissue by targeting a number of substrates.

Role of reproductive hormones: Reproductive hormone axis alterations have been reported to occur commonly in both women and men with epilepsy. In men, the most common reported manifestations are decreased sexual function with decreased libido and/or impotence while women often have menstrual cycle irregularities and may have increased risk of infertility or signs of hyperandrogenism.

Hypogonadotropic hypogonadism is the common disorder caused by abnormal reproductive functions in epilepsy patients and has been found to be more common in women with right temporal lobe epilepsy compared to left temporal lobe epilepsy. Hypothalamic amenorrhea is the most frequent form of this in women with epilepsy, which is characterized by amenorrhea associated with low gonadotropin and estrogen levels and diminished LH response to gonadotropin Releasing Hormone (GnRH).

Many studies indicate that women with idiopathic generalized epilepsy have higher pulse frequency GnRH secretion than normal controls.
Table 1: Inherited epilepsies with their loci and causative genes

<table>
<thead>
<tr>
<th>Inherited epilepsies</th>
<th>Chromosomal locus</th>
<th>Gene</th>
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<tbody>
<tr>
<td>BNFC type1</td>
<td>20q13.2</td>
<td>KCNQ2</td>
</tr>
<tr>
<td>BNFC with myokymia</td>
<td>20q13.2q</td>
<td>KCNQ2</td>
</tr>
<tr>
<td>BNFC type2</td>
<td>8q24</td>
<td>KCNQ3</td>
</tr>
<tr>
<td>Benign familial neonatal infantile seizures</td>
<td>2q24</td>
<td>SCN2A</td>
</tr>
<tr>
<td>Febrile seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEFS+type 1</td>
<td>19q13.1</td>
<td>SCN1B</td>
</tr>
<tr>
<td>GEFS+type 2</td>
<td>2q24</td>
<td>SCN1A</td>
</tr>
<tr>
<td>GEFS+type 3</td>
<td>5p31.1-q33.1</td>
<td>GABRG2</td>
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<tr>
<td>Febrile seizures associated with afebrile seizures</td>
<td>2q24</td>
<td>SCN2A</td>
</tr>
<tr>
<td>Severe myoclonic epilepsy of infancy</td>
<td>2q24</td>
<td>SCN1A</td>
</tr>
<tr>
<td>Intractable childhood epilepsy with frequent generalized tonic-clonic seizures</td>
<td>2q24</td>
<td>SCN1A</td>
</tr>
<tr>
<td>ADNFLE type 1</td>
<td>20q13.2-q13.3</td>
<td>CHRNA4</td>
</tr>
<tr>
<td>ADNFLE type 2</td>
<td>15p24</td>
<td>?</td>
</tr>
<tr>
<td>ADNFLE type 3</td>
<td>1q21</td>
<td>CHRNA2B</td>
</tr>
<tr>
<td>Absence epilepsy</td>
<td></td>
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</tr>
<tr>
<td>Childhood absence epilepsy type1</td>
<td>8q24</td>
<td>?</td>
</tr>
<tr>
<td>Childhood absence epilepsy type2</td>
<td>5q31.1-q33.1</td>
<td>GABRG2</td>
</tr>
<tr>
<td>Childhood absence epilepsy type3</td>
<td>3q27.1</td>
<td>CLCN2</td>
</tr>
<tr>
<td>Juvenile absence epilepsy</td>
<td>3q27.1</td>
<td>CLCN2</td>
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<tr>
<td>Myoclonic epilepsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile absence epilepsy</td>
<td>3q27.1</td>
<td>CLCN2</td>
</tr>
<tr>
<td>Myoclonic epilepsy of Lafora</td>
<td>6q24</td>
<td>EPM2A</td>
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<tr>
<td>Other epilepsy syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy with grand mal seizures on awakening</td>
<td>3q27.1</td>
<td>CLCN2</td>
</tr>
<tr>
<td>Autosomal dominant lateral temporal lobe epilepsy</td>
<td>10q24</td>
<td>LGII</td>
</tr>
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Many other reproductive disorders prevail more frequently in epilepsy patients. Premature menopause occurs more commonly in women with epilepsy. Another endocrine disorder, Polycystic Ovarian Syndrome (PCOS), occurs in approximately 4-7% of women of reproductive age in the general population, but in 10-25% of women with Epilepsy. According to Herzog et al., PCOS occurs more commonly in women with TLE than in the general female population (Pennell, 2009).

**Molecular basis of epilepsy:** As epilepsy is a neurological disorder caused by rapid firing of the neurons in CNS and ion channels are directly involved in neuronal excitability, therefore ion channel mutations are associated with inherited epilepsy. Among the listed disorders in the Table 1, 19 disorders are caused by mutations in genes encoding 11 different ion channels and 6 other genes that do not have well-defined functions.

There exists a considerable genetic heterogeneity among the inherited epilepsies i.e., same clinical syndrome may be caused by mutations of different genes. For instance, GEFS+ is caused by mutations in two voltage-gated sodium channel genes SCN1B and SCN1A or in the gene encoding the γ subunit of γ amino butyric acid (GABAA) receptors (GABRG2). Mutations of another sodium channel gene (SCN2A) are associated with a very similar syndrome. On the other hand, ADNFLE is caused by mutations in genes encoding different subunits of nicotinic acetylcholine receptors (nAChRs) and childhood absence epilepsy, caused by mutations of the CLCN2 chloride channel gene or GABRG2.

**Epilepsy associated with voltage-gated potassium channels:** The genetically heterogeneous syndrome of BFNC has an identified locus on chromosomes 8q and 20q. In 1998, Potassium channel gene KCNQ2 was identified for the 20q-linked BFNC and KCNQ3 as responsible for the chromosome 8 q-linked BFNC.

These potassium channels, KCNQ3 and KCNQ2, exhibit a high amino acid sequence identity with another voltage-gated potassium channel gene KCNQ1 which cause a congenital long QT syndrome. The KCNQ2 and KCNQ3 potassium channels generate ionic currents similar to the M-currents generated by neurons in brain. KCNQ2 or KCNQ3 mutations reduce function of the potassium channel by a mechanism consistent with the autosomal dominant inheritance pattern of BFNC.

**Epilepsy associated with voltage-gated sodium channels:** GEFS+ epilepsy is associated with voltage gated sodium channels. Most of the GEFS+ cases are reported with missense mutations in SCN1A gene which encodes a neuronal voltage-gated sodium channel α subunit but SCN1B and SCN2A and a GABA receptor subunit gene GABRG2 can also cause the GEFS+ syndrome. Different SCN1A mutations associated with severe myoclonic epilepsy of infancy encode nonfunctional sodium channels which suggest that this disorder is caused by loss-of-function mutations (Baulac et al., 2008).
ADNFLE is also associated with voltage gated sodium channels and caused by mutations in two genes CHRNA4 and CHRN2B encoding distinct nAChR subunits (α4 and β2). In an Australian family, C→T transition was identified which caused the replacement of serine with phenylalanine in 252 codon of the CHRNA4.

A second mutation in the same axon has been reported in a Norwegian family. ADNFLE is also genetically heterogeneous as it is linked to two chromosome loci 15q 24 and 20q 13.3 (Saenz et al., 1999).

**Epilepsies associated with voltage-and ligand-gated chloride channels:** Many research studies provide evidences of inherited epilepsy association with mutations in two genes that encode subunits of GABAA receptors and a gene that encodes a voltage-gated chloride channel. The GABAA receptors are composed of five subunits encoded by multiple different gene families (α, β, γ, π, θ, ε and δ). The gene encoding the α1 subunit (GABRA1) has been linked to juvenile myoclonic epilepsy while mutations in GABRG2 encoding the γ2 subunit of the GABA_A receptors have been associated with GEFS+ and childhood absence epilepsy with febrile seizures.

The third gene encoding a voltage-gated chloride channel associated with inherited epilepsy is CLCN2. CLCN2 mutations have been associated with idiopathic generalized epilepsy in three families which exhibit multiple seizure phenotypes including juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy and epilepsy with grand mal seizures on awakening.

**Prevention of epilepsy:** Epilepsy is causing severe threats to human health so it must be prevented for advancement of human life. It seems to be the disease in which the physicians wait to treat the symptoms until the disorder develops in the patient. Prevention of this severe and common disease has not been a major focus of the research although it takes time to develop and risks can be easily identified at early stages. Patients with moderate to severe head injury, brain tumors, intra cerebral hemorrhage, chronic neurodegenerative diseases, dysplastic brains and children with prolonged febrile seizures can be identified with relatively high risk for epilepsy.

Therefore, it is appropriate to propose the new syndrome, the Risk of Epilepsy Development (RED) syndrome. This syndrome identifies that epilepsy begun to develop after a variety of brain injuries like trauma, ischemia, central nervous system infection and some forms of chronic neurodegeneration.

It is necessary to understand the process of epileptogenesis in order to develop strategies for the prevention of epilepsy. In initial stages, a normal brain experiences an injury which can be due to trauma, infection, ischemia, status epilepticus, or the presence of a malformation. In response to these injuries, the brain attempts to repair but after some period of time, hyperexcitability develops and seizures begin to occur and continue to produce the damage. While going to develop an antiepileptogenic therapy, one must keep in mind that even suppression of small seizures can interfere with the process of epileptogenesis, therefore, in this case, significant antiseizure drug therapy may also be antiepileptogenic.

**REFERENCES**


