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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).

There are many condition that are related symptomatically with epilepsy such as Alzheimer disease, Cretic fedth Jacob disease, Lennox gastuate syndrome, in these the myclonus seizure are mostly occur, but there treatment, Clinical presentation and prognosis are widely different.

The purpose of the review is to study the pathophsiology 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).

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

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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 mild 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 amenorrhe 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

Inherited epilepsies		
Syndrome	Chromosomal locus	Gene
BNFC		
BNFC type1	20q13.2	KCNQ2
BNFC with myokymia	20q13.2q	KCNQ2
BNFC type2	8q24	KCNQ3
Benign familial neonatal infantile seizures	2q24	SCN2A
Febrile seizures		
GEFS+type 1	19q13.1	SCN1B
GEFS+type2	2q24	SCN1A
GEFS+type3	5q31.1-q33.1	GABRG2
Febrile seizures associated with afebrile seizures	2q24	SCN2A
Severe myoclonic epilepsy of infancy	2q24	SCN1A
Intractable childhood epilepsy with frequent generalized tonic-clonic seizures	2q24	SCN1A
ADNFLE		
ADNFLE type1	20q13.2-q13.3	CHRNA4
ADNFLE type2	15q24	?
ADNFLE type3	1q21	CHRNB2
Absence epilepsy		
Childhood absence epilepsy type1	8q24	?
Childhood absence epilepsy type2	5q31.1-q33.1	GABRG2
Childhood absence epilepsy type3	3q27.1	CLCN2
Juvenile absence epilepsy	3q27.1	CLCN2
Myoclonic epilepsy		
Juvenile absence epilepsy	3q27.1	CLCN2
Myoclonic epilepsy of Lafora	6q24	EPM2A
Other epilepsy syndromes		
Epilepsy with grand mal seizures on awakening	3q27.1	CLCN2
Autosomal dominant lateral temporal lobe epilepsy	10q24	LGI1

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^2 subunit of γ amino butyric acid (GABAA) receptors (*GABRG*2). 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 *CLCN*2 chloride channel gene or *GABRG*2.

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 CHRNB2 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 *CHRNA*4.

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 (*GABRA*1) has been linked to juvenile myoclonic epilepsy while mutations in *GABRG*2 encoding the γ^2 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

Baulac, S., I. Gourfinkel-An, P. Couarch, C. Depienne, A. Kaminska, O. Dulac, M. Baulac, E. LeGuern and R. Nabbout, 2008. A novel locus for generalized epilepsy with febrile seizures plus in french families. Arch. Neurol., 65(7): 943-951.

Becker, E.B. and A. Bonni, 2004. Cell cycle regulation of neuronal apoptosis in development and disease. Prog. Neurobiol., 72: 1-25.

Beleza, P., 2009. Refractory epilepsy: A clinical oriented review. Eur. Neurol., 62: 65-71.

Berg, A.T., 2011. Epilepsy, cognition and behavior: The clinical picture. Epilepsia, 52: 7-12.

Camfield, C.S., P.R. Camfield and P.J. Veugelers, 2002. Death in children with epilepsy: A population-based study. Lancet, 359(9321): 1891-1895.

Crino, P.B., H. Miyata and H.V. Vinters, 2002. Neurodevelopment disorders as a cause of seizures: Neuropathologic, genetic and mechanistic considerations. Brain Pathol., 12: 212-233.

Donner, E.J. and O.C. Snead, 2006. New generation anticonvulsants for the treatment of epilepsy in children. NeuroRx, 3(2): 170-180.

Hader, W.J., M. Mackay, H. Otsubo, S. Chitoku, S. Weiss, L. Becker, O.C. Snead 3rd and J.T. Rutka, 2004. Cortical dysplastic lesions in children with intractable epilepsy: Role of complete resection. J. Neurosurg., 100: 110-117.

Hannan, A.J., S. Servotte, A. Katsnelson, S. Sisdiya, C. Blakemore, M. Squier and Z. Molnár, 1999. Characterization of nodular neuronal heterotopia in children. Brain, 122: 219-238.

Hauser, W.A., J.F. Annegers and L.T. Kurland, 1993. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia, 34(3): 453-468.

Hua, Y. and P.B. Crino, 2003. Single cell lineage analysis in human focal cortical dysplasia. Cereb. Cortex, 13: 693-699.

Pennell, P.B., 2009. Hormonal aspects of epilepsy. Neurol. Clin., 27: 941.

Pillai, J.J., R.B. Hessler, J.D. Allison, Y.D. Park, M.R. Lee and T. Lavin, 2002. Advanced MR Imaging of cortical dysplasia with or without neoplasm: A report of two cases. Am. J. Neuroradiol., 23: 1686-1691.

Saenz, A., J. Galan, C. Caloustian, F. Lorenzo, C. Marquez, N. Rodrıguez, M.D. Jimenez, J.J. Poza, A.M. Cobo, D. Grid, J.F. Prudhomme and A.L. Munain, 1999. Autosomal dominant nocturnal frontal lobe epilepsy in a Spanish family with a Ser252Phe mutation in the CHRNA4 gene. Arch. Neurol., 56(8): 1004-9.

Saneto, R.P. and E. Wyllie, 2000. Epilepsy surgery in infancy. Semin. Pediatr. Neurol., 7: 187-193.

Schwartzkroin, P.A. and C.A. Walsh, 2000. Cortical malformations and epilepsy. Ment. Retard. Dev. D. R., 6(4): 268-280.

Shinnar, S. and J.M. Pellock, 2002. Prognosis of pediatric epilepsy. J. Child Neurol., 17S1: S4-17.

Van De Graff, K., 2000. Human Anatomy. 5th Edn., McGraw Hill, New York.

Wong, M., 2007. Mechanisms of epileptogenesis in tuberous sclerosis complex and related malformations of cortical development with abnormal glioneuronal proliferation. Epilepsia, 48: 617-630.