INTRODUCTION

Epilepsy is a neurological disorder, characterized by recurrent unprovoked seizures which have a high impact on the individual as well as on society as a whole. In addition to the economic burden, epilepsy imposes a substantial burden on the patient and their surroundings. Idiopathic epilepsy tends to appear during childhood or adolescence although it may not be diagnosed until adulthood. In this type of epilepsy, there are no brain or spinal cord abnormalities. The brain is structurally normal on a brain magnetic resonance imaging (MRI) scan. Although special studies may show subtle change in the brain that may have been present since birth ***(de Kinderen et al., 2011).***

Vitamin D is fat soluble vitamin that present in vary few foods and available as a dietary supplement. It's also produced endogenously when ultraviolet rays strike the skin and trigger vitamin D synthesis ***(Stolzenberg – Solomon et al., 2006).***

Measurement of circulating 25 (OH) vitamin D concentration is *recognized* as the best function measure of vitamin D status ***(Joyce and Broce, 2008).***

There is evidence which suggests that the active form of vitamin D is involved in development of adult brain function ***(Garcion et al., 2002)***. Metabolic pathways for vitamin D have been found in the hippocampus and cerebellum ***(Eyles et al.,***

2005) suggesting that vit D may be active in areas of the brain involved in planning, processing and formation of new memories ***(Buell et al., 2009).***

Przybelski and Binkley (2007) suggested a potential role for vitamin D in cognitive function of older adults as they reported positive significant correlation between serum 25(OH)D concentration and mini-mental state examination score (MMSE) in patients suffering from memory problems.

Vitamin D deficiency was associated with low mood and with impairment on two of four measures of cognitive performance ***(Wilkins et al., 2006).*** Additionally, ***Joyce and Bruce (2008)*** concluded that there is ample biological evidence to suggest an important role for vitamin D in brain development and function.

AIM OF THE WORK

This study aim to evaluate the effect of Vit D supplementation on cognitive functions in idiopathic epileptic children as well as effect of vit D on seizures control in the same patients.

Chapter One

EPILEPSY

The term epilepsy includes a number of different syndromes the main feature of which is a predisposition to recurrent unprovoked seizures. Seizures in turn are sudden, brief attacks of altered consciousness; motor, sensory, cognitive, psychic or autonomic disturbances; or inappropriate behavior caused by abnormal excessive or synchronous neuronal activity in the brain ***(Fisher et al., 2005)***.

The phenotype of each seizure is determined by the point of origin of the hyperexcitability and its degree of spread in the brain. By agreement, the diagnosis of epilepsy requires that the patient has had at least two unprovoked seizures ***(Kwan and Brodie, 2006)***.

An epileptic syndrome is characterized by a cluster of signs and symptoms usually occurring together, including type of seizure(s), etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and sometimes prognosis ***(William et al., 2009)***.

About 50 million people worldwide have epilepsy with almost 80% of these people being in developing countries ***(WHO, 2001).*** In Egypt, the prevalence was 6.98 / 1000 ***(Tallawy et al., 2010).***

Mechanisms:

The pathophysiology of epilepsy involves alterations of normal physiological processes. An epileptic seizure is produced by synchronous and sustained firing of a population of neurons in the brain. Epileptogenicity refers to the excitability and synchronization of neuronal networks that produce epileptiform activity in the brain. Both excitatory and inhibitory influences may be altered, creating a predisposition to excessive synchrony within neuronal populations ***(Foldvary-Schaefer and Wyllie, 2007).***

Multiple factors contribute to epileptogenesis such as intracellular, intrinsic membrane, and extracellular mechanisms. Three key elements contribute to the development of the hyperexcitability needed for epileptogenesis: 1) the capability of membrane in pacemaker neurons to develop intrinsic burst discharges; 2) the reduction of gamma-amino-butyric acid (GABA) inhibition; and 3) enhancement of synaptic excitation through recurrent excitatory circuits ***(Najm et al., 2007)***.

Function of ion channels:

The neuronal cytoplasmic membrane consists of a lipid bilayer that is largely impermeable to ions. However ions can be actively transported across the membrane by pumps and can move through voltage-gated or ligand-gated channels depending on their electrochemical gradients. The ionic pumps create and maintain the resting membrane potential, whereas

the ionic currents flowing through the gated channels lead to changes in the excitation state ***(Avanzini et al., 2013).***

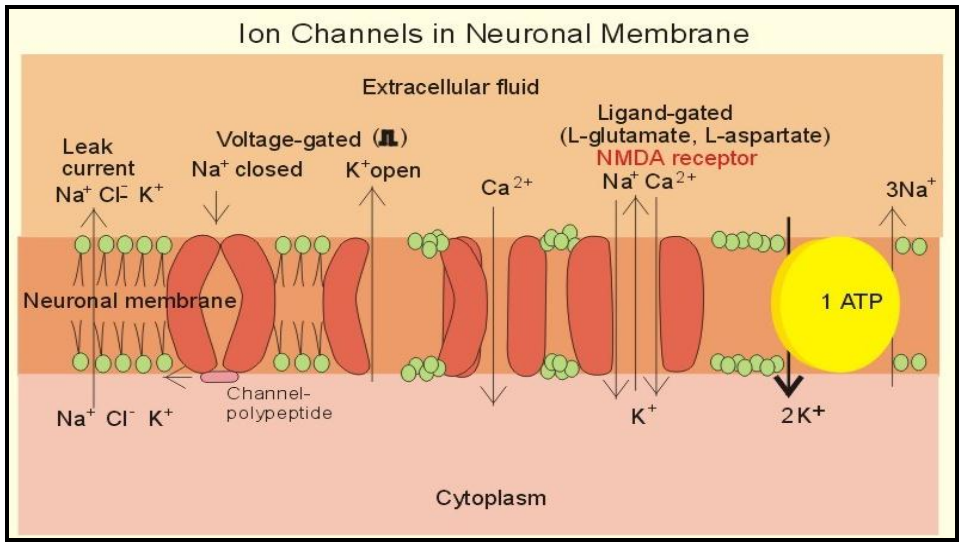

Figure (1): Ion channels in neuronal membrane ***(Avanzini et al., 2013).***

Reduction in extracellular space induces seizure like activity that is independent of chemical synaptic mechanisms. The repetitive synaptic activation of cortical neurons and the intense synchronous activity during epileptic events are associated with an increase in extracellular potassium and decrease in extracellular calcium. Increased [K^+] was shown in induce interictal spikes that leads to seizure activity. On the other hand, decrease in [Ca^{++}] increases membrane excitability. These two phenomena, when they occur together, were shown to increase significantly the seizure susceptibility in hippocampus ***(Najm et al., 2007)***.

Neurotransmission:

1) Excitatory neurotransmission:

A. Glutamate: excitatory neurotransmissions in the brain are mediated largely by the excitatory amino acid glutamate.

Glutamate the naturally occurring neurotransmitter; is a flexible molecule that can bind to its receptors cause influx of sodium ions (Na^+) through the receptor's pore producing a fast excitatory postsynaptic potential often followed by an action potential ***(Najm et al., 2007).***

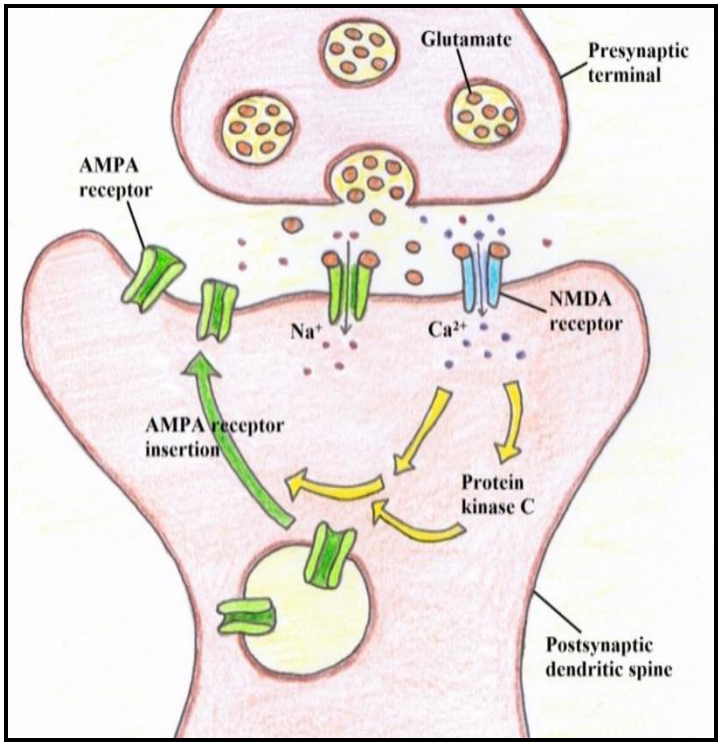

Figure (2): Gultamate release in the presynaptic terminals ***(Najm et al., 2007).***

B. Acetylcholine: has a modulatory role in epilepsy through its muscarinic receptors. It acts as an excitatory neurotransmitter in cerebral cortex and limbic system, and these excitatory paths may be involved in the propagation of seizures ***(Naim et al., 2002).***

2) Inhibitory neurotransmission:

A. The primary inhibitor transmitter in the brain is GABA. GABA is synthesized from glutamate in the presynaptic terminal by action of the enzyme glutamic acid decarboxylase (GAD), which requires pyridoxine (vitamin B6) as a cofactor. Influx of Ca^{2+} caused by depolarization of the terminal prompts vesicles to release GAD into the synaptic cleft. GABA diffuses across the cleft and binds to its receptors (GABAa) which opens a pore or channel through which chloride ions (Cl^-) enter the neuron. This Cl^- influx increases the negative charge inside the postsynaptic neuron, thereby hyperpolarizing it ***(Jones et al., 2005)***.

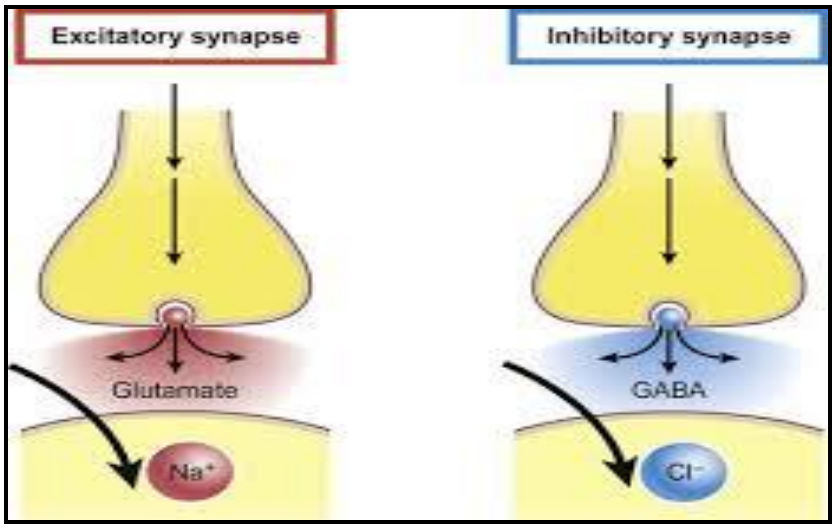

Figure (3): Excitatory synapse versus Inhibitory synapse ***(Jones et al., 2005).***

The resultant change in membrane potential is called an inhibitory postsynaptic potential which reduces firing of the neuron by temporarily keeping the membrane potential away from firing threshold. Obviously, a reduction of any component of the GABA inhibitory postsynaptic potential system favors excitation and predisposes to epileptic firing. Conversely, enhancing the GABA system is a logical approach for restraining neuronal hyperexcitability ***(Jones et al., 2005).***

B. Adenosine is an endogenous neuromediator with inhibitory effects on brain function. One of the most important actions of the adenosine receptor (mainly A1 receptor) is a reduction in excitatory transmission and in postsynaptic excitability ***(Woert et al., 2006)***.

Diagnosis:

A- Clinical diagnosis:

The diagnosis of a seizure can be made clinically in most cases by obtaining a detailed history and performing a general clinical examination with emphasis on neurological and psychiatric status.

The history should cover the existence of prenatal and perinatal events, spontaneous abortions, seizures in the new born period, febrile seizures, any unprovoked seizures and epilepsies in the family. A history of prior head trauma, infection, or toxic episodes must be sought and evaluated. A family history of seizures or neurological disorders is significant ***(Chang and Lowenstein, 2003)***.

B- Appropriate studies:

The EEG is an essential component in the evaluation of epilepsy which provides important information about epileptiform discharges and is required for the diagnosis of specific electro-clinical syndromes ***(Nolan et al., 2004)***.

Because an EEG taken during a seizure free interval is normal in 30% of patients, one normal EEG does not exclude epilepsy. A second EEG performed during sleep in sleep-deprived patients reveals epileptiform abnormalities in half of patients whose first EEG was normal. Rarely repeated EEGs

are normal and epilepsy may have to be diagnosed on clinical grounds ***(Chang and Lowenstein, 2003)***.

Table (1): Studies in patients with new-onset epilepsy

Magnetic resonance imaging (MRI)	Each patient with new onset epilepsy should have an MRI to detect structure lesions caused by for example cortical malformation, traumatic brain injury, brain tumor, and cerebrovascular disease, which are the most common causes of symptomatic epilepsy. Contrast media, inversion recovery, fast field echo and 3D only in special cases. Evenin idiopathic epilepsy, MRI is recommended to diagnose unsuspected dual pathology as discussed above
Electroencepthalogram (EEG)	Each patient with new onset epilepsy should have an EEG. EEG is most valuable within 24h of the seizure. Information gain is optimal up to the 4^{th} EEG, if no paroxysmal interictal discharges are found, repeat EEG during sleep. 24-hour EEG most meaningful in a patient with frequent seizures who can be expected to have seizures during the 24h recording. Interictal EEG discharges may support the diagnosis of the epilepsy syndrome.
Computer tomogram (CT)	Computer tomograms are obsolete, except to detect fractures or hemorrhage in an emergency situation.
HEAD X-ray	Obsolete
Clinical chemistry	Routine work-up, creatin kinase, Vitamin B6 if seizures are unresponsive to AEDs, even in adults. CSF, only when infectious disorders are suspected. Creatin kinase increased within 12-24h, prolactin increased within 30 min.
Single-photon emission-tomogram (SPECT) and postion-emission-tomogram (PET), magneto encephalography (MEG)	Only for pre-surgical work-up or scientific studies.

(Elger and Schmidt, 2008)

Classification of epileptic seizures:

The International League against Epilepsy (ILAE) presents a revised operational classification of seizure types. The purpose of such a revision is to recognize that some seizure types can have either a focal or generalized onset, to allow classification when the onset is unobserved, to include some missing seizure types and to adopt more transparent names ***(ILAE, 2016)***.

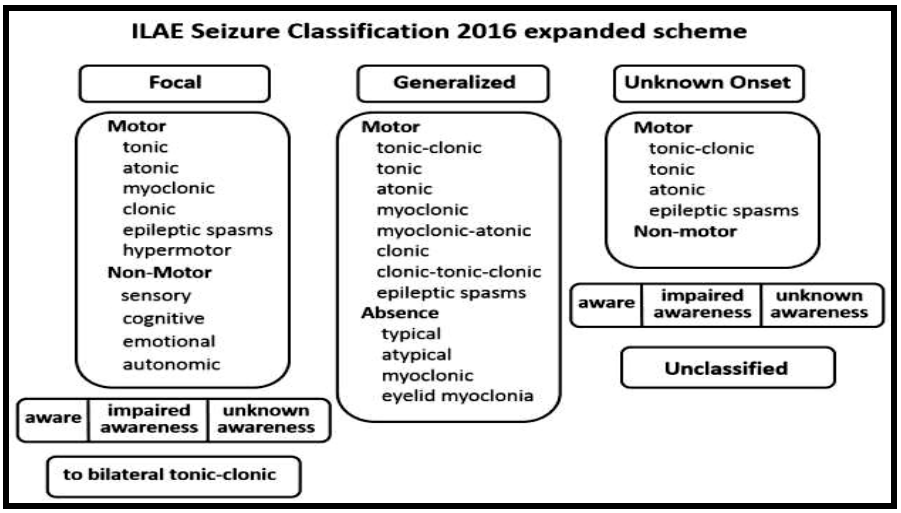

Figure (4): The ILAE 2016 Operational Classification of Seizure Types: Basic and Expanded Scheme ***(ILAE, 2016).***

So In their recent report, the ILAE Commission for Classification of the Epilepsies has addressed etiology and divided epilepsies into three categories (genetic, structural/metabolic, unknown cause) ***(Shorvon, 2011).***

Table (2): ILAE revised terminology for organization of seizures and epilepsies 2011-2013

Major changes in terminology and concepts		
New term and concept	Examples	Old term and concept
Etiology (an individual may fit into more than one group)		
Genetic: genetic defect directly contributes to the epilepsy and seizures are the core symptom of the disorder	Channelopathies, GLUT1 deficiency, etc	**Idiopathic:** presumed genetic
Structural: caused by a structural disorder of the brain	Tuberous sclerosis, cortical malformations, mesial temporal lobe epilepsy with hippocampal sclerosis (MTE with HS), gelastic seizures with hypthalmic hamartoma	Symptomatic: secondary to a known or presumed disorder of the brain
Metabolic: caused by a metabolic by a metabolic disorder of the brain	Pyoxidine deficiency, GLUT1 deficiency, etc	Symptomatic
Immune: epilepsy with evidence of autoimmune mediated CNS inflammation	NMDA receptor antibody encepthalitis, voltage gated potassium channel antibody encephalitis	Symptomatic
Infectious: an infectious etiology refers to a patient with epilepsy, rather than seizures occurring in the setting of acute infection such as meningitis or encephalitis. These infections sometimes have a structural correlate.	Tuberculosis, HIV, cerebral malaria, neurocysticecrosis, subacute sclerosing panencephalitis, cerebral toxoplasmosis	
Unknown: the cause of epilepsy is unknown		**Cryptogenic:** presumed symptomatic

(Shorvon, 2011)

The ILAE Classification Commission report suggested that the terms idiopathic, symptomatic, and cryptogenic are replaced by the terms genetic, structural/metabolic, and unknown. This classification is hard to be followed for many reasons Firstly, the term idiopathic has been honored in history and should be replaced only if there are major advantages to doing so, and there is widespread disagreement about the need for this change ***(Ferrie, 2010; Guerrini, 2010; Wolf, 2010).***

Furthermore, the idiopathic epilepsies are due in all likelihood to a combination of genetic and environmental influences (epistatic and epigenetic influences, particularly in development), and although genetic influences probably predominate, these have proved largely conjectural. There are also many genetic causes of ‘‘symptomatic epilepsy.’’ For these reasons, the term idiopathic seems worthy of retention. Similarly, replacing the term ‘‘symptomatic’’ by ‘‘structural/metabolic’’ also seems largely unnecessary, not the least because many of the symptomatic conditions are neither structural nor metabolic, in the normal sense of these words. Replacing the term ‘‘cryptogenic epilepsy’’ with ‘‘epilepsy of unknown cause’’ seems also simply to anglicize and remove the venerable Greek origin to the word, rather than to change the conceptual basis in any meaningful way ***(Shorvon, 2011).***

Table (3): Suggested scheme for etiologic classification of epilepsy related to both old and new classification

Main category	Subcategory	Examples*
Idiopathic epilepsy	Pure epilepsies due to single gene disorders	Benign familial neonatal convulsions; autosomal dominant nocturnal frontal lobe epilepsy; generalized epilepsy with febrile seizures plus; severe myoclonic epilepsy of childhood; benign adult familial myoclonic epilepsy
	Pure epilepsies with complex inheritance	Idiopathic generalized epilepsy (and its subtypes); benign partial epilepsies of childhood
Symptomatic epilepsy		
Predominately genetic or developmental causation	Childhood epilepsy syndromes	West syndrome; Lennox-Gastaut syndrome
	Progressive myoclonic epilepsies	Unverricht-Lundborg disease; Dentato-rubro-pallido-luysian atrophy; Lafora body disease; mitochondrial cytopathy; sialidosis; neuronal ceroid lipofuscinosis; myoclonus renal failure syndrome
	Neurocutaneous syndromes	Tuberous sclerosis; neurofibromatosis; Sturge-Weber syndrome
	Other neurologic single gene disorders	Angelman syndrome; lysosomal disorders; neuroacanthocytosis;organic acidurias and peroxisomal disorders; prophyria; pyridox inedependent epilepsy; Rett syndrome; Urea cycle disorders; Wilson disease; disorders of cobalamin and folate metabolism
	Disorders of chromosome function	Down syndrome; Fragile X syndrome; 4p-syndrome; isodicentric chromosome 15; ring chromosome 20
	Developmental anomalies of cerebral structure	Hemimegalencephaly; focal cortical dysplasia; agyria-pachygyria-band spectrum; agenesis of corpus callosum; polymicrogyria; schizencephaly; periventricular nodular heterotopia; microcephaly; arachnoid cyst
Predominately acquired causation	Hippocampal sclerosis	Hippocampal sclerosis
	Perinatal and infantile causes	Neonatal seizures; postneonatal seizures; cerebral palsy; vaccination and immunization
	Cerebral trauma	Open head injury; closed head injury; neurosurgery; epilepsy after epilepsy surgery; nonaccidental head injury in infants
	Cerebral tumor	Glioma; ganglioglioma and hamartoma; DNET; hypothalamic hamartoma; meningioma; secondary tumors