Introduction

Epilepsy is one of the most common and challenging neurological disorders affecting children. The cumulative life time incidence of epilepsy is now considered to be 3% where more than half of the cases begin in childhood ***(Johnston, 2004).***

Epilepsy has been defined as recurrent convulsive and non convulsive seizures caused by partial or generalized epileptogenic discharge in the cerebrum ***(John et al., 2000).***

Neuropeptides act as cotransmitters of classical neurotransmitters. Like classical transmitters they become released during epileptic seizures. Interesting acute seizures induce over-expression of some of these peptides (e.g. neurokinin B, somatostatin, cholecystokinin, dynorphin, neuropeptide Y) in brain areas involved in limbic seizures ***(Gruber, 1993).***

Neruopeptide Y : (NPY) is a 36 amino acid peptide made by neurons throughout the brain and by other secretory cells of the body ***(William et al., 2003).*** Neroupeptide Y has been associated with number of physiologic processes in the brain, including the regulation of energy balance, memory and learning. In the hippo campus and neocortex, NPY is made by neurons that almost all express gamma amino butyric-acid ***(William et al., 2003).***

There is a probable modulatory effects of NPY in brain structures, involved in initiation, propagation or control of seizures ***(Reibel et al, 2001).***

Neuropeptide Y is known to regulate the presynaptic glutamate release and neuronal responses to excitatory neurotransmission ***(Wang, 2005).***

Aim of the Work

The aim of this work is to evaluate the relationship between type of seizure, its frequency, aetiology, the antiepileptic drugs used and serum level of neuropeptide Y in epileptic children.

Epilepsy

Definition:

Epilepsy is a frequent neurological disease in childhood characterised by recurrent seizures and sometimes with major effects on social, behavioural and cognitive development ***(Lagae, 2008).***

- A seizure or convulsion is a paroxysmal; time limited change in motor activity and /or behavior that result from abnormal electrical activity in the brain ***(Johnston, 2004).***

Epidemiology of Epilepsy:

Seizures are common in the pediatric age group & occur in approximately 10% of children ***(Johnston, 2004).***

Whereas all patients with epilepsy have seizures many more patients with epilepsy have a single seizure during life and are not considered to have epilepsy ***(Nancy and Elaine, 1999).***

More recent estimates of the prevalence of single and recurrent non febrile seizures in children younger than 10 years of age range from 5.2 to 8.1 per 1,000 ***(Menkes, 2000).***

Generalized seizures and epilepsy syndrome types are more prevalent in children 0-6 years of age, while partial/

localization types are prevalent in children aged 6-15 years ***(Eriksson and Koivikko, 1999).***

Over all at least 30% of patients with epilepsy continue to have seizures despite optimal drug therapy ***(Hauser et al., 1998).***

Intractability is defined requiring two antiepileptic, at least one seizure per month for 18 months and no seizure free periods longer than three months during that time ***(Berg, 2006).***

Genetics of Epilepsy:

In recent years, different mutations in genes that control the excitability of neurons have been described in idiopathic childhood epilepsies. Most commonly, sodium/potassium channelopathies and GABA-receptor mutations are involved. Major progress has been made in the field of idiopathic generalised epilepsies associated with febrile seizures (GEFS+). It is now becoming clear that mutations should not only be looked for in familial cases, but also in sporadic cases, especially in infants and young children with unexplained severe epileptic encephalopathies. Many studies also define 'epilepsy susceptibility genes', which contribute to one's individual genetic vulnerability to develop epilepsy. It should be realized, however, that in the most common idiopathic benign childhood epilepsies (benign rolandic and occipital epilepsies), major breakthroughs are still awaited. In addition, a better clinical description of the epileptic phenotypes is needed

to explain more precisely the genotypic and phenotypic heterogeneity.

Genetic studies are nowadays becoming a necessary diagnostic step in the evaluation of idiopathic childhood epilepsies, not only in familial cases, but also in sporadic cases ***(Lagae, 2008).***

Basic Mechanism of Epilepsy:

Epilepsy is a paroxysmal disorder characterized by abnormal neuronal discharges. Although the causes of epilepsy are many, the fundamental disorder is secondary to abnormal synchronous discharges of network of neurons. Epilepsy can be secondary to either abnormal neuronal membrane or an imbalance between excitatory and inhibitory influences ***(Holmes and Ben-Ari, 2001).***

Pathophysiology of Epilepsy:

1. Excitation and inhibition of neuronal membrane:

Neuronal membrane consists of lipid bilayers mixed with proteins that traverse the membrane and form ion channels. Each neuron has a resting potential that represent the voltage difference exists because of the separation of positive and negative changes across the cell membrane. The extracellular space along the membrane is dominated by Na^+ and Cl^- ions, whereas K^+, proteins, and organic acids are found in the intracellular space. Membranes are permeable to Na^+, Cl^-, and K but impermeable to large organic ions and proteins.

Because the lipid bilayers act as barrier to the diffusion of ions, a net excess of positive charges outside and negative charges inside produces a resting membrane potential of approximately -50 to-80Mv.Ion leaks across the membrane occur moving from high concentration to low concentration: Na^+ leaks in K^+ out ***(Ganong, 2000).*** The $Na^+ – K^+$ pump extrudes Na from the cell and brings in K^+, counterbalancing the leakage. The pumps, which move Na^+ and K^+ against their net electrochemical gradients, require energy that is derived from hydrolysis of adenosine triphophosphate. A reduction in the negativity of this polarized state is called depolarization; an increase in the negativity of the resting potential is known as hyper polarization. Membrane permeability changes that allow Na^+ to enter the cell lead to depolarization, and membrane changes that allow K^+ to exit the cell or Cl^- to enter the result in hyper polarization***. (Jin and Wang, 2002).***

2. Excitation and inhibition of neurons by neurotransmitters:

Proteins segments extend out of the membrane and serve as receptor sites. Inotropic receptors directly alter the conductance of the ion channel when bound to a neurotransmitter. Examples of inotropic receptors include the gamma aminobutyric acid (GAB_A) receptor that increases Cl^- conductance and the N-methyl-D-aspartate (NMDA) receptor that increases permeability to Na^+ and Ca^{++} neurotransmitters (such as GABA)that cause hyper polarization of the neurons give rise to inhibitory postsynaptic potential (IPSPs), which result in a greater intracellular negativity than baseline.

Neurotransmitter that lead to depolarization (such as excitatory amino acids) give rise to excitatory postsynaptic potential (EPSPs) which result in an inward flow of positive charges through synaptic membrane, leaving a relatively negative extracellular environment whether a neuron generates an action potential is determined by relative balance of EPSPs and IPSPs ***(Kandel et al., 2000).***

A second type neurotransmitter is the metabotropic receptor. When a transmitter binds to the metabotropic receptor, it activates a second messenger system (guanyl nucleotide – bending protein (G-protein). The activated G-protein then open an ion channel or activate an enzyme, such as a cyclase (cyclic adenosine monophosphate) or hydrolase, to affect the generation of additional messenger molecules within a cell. Examples of receptors that activate 2^{nd} messenger systems include $GABA_B$ receptors, peptide and catecholaminergic receptors, and the metabotropic receptors activated by glutamate not that $GABA_A$ receptors are ionotropic receptors that enhance Cl^- conductance, and $GABA_B$ receptors are metabotropic that are coupled through G proteins to calcium or K^+ ion channels ***(Schousboe, 2002).***

3. Generation of Seizure Activity:

Although the events that lead from the interictal to ictal state are not well understood, a number of possible mechanisms may be involved. These abnormalities may include disturbance of the neuronal membranes or excitatory or inhibitory

neurotransmitter. Decreases in synaptic inhibition, increases in synaptic excitation, alteration in K^+ or Ca^{++} currents, or changes in the extacellular ions concentrations may trigger prolonged depolarization. These changes may occur not only in the microenviroment at the epileptic focus, but also at distant sites through synaptic pathways. These "downstream" changes may be responsible for the generalization of the seizures. Different behavior and AAG features of the seizures depend on spread of the discharge and which specific cortical or subcortical nuclei developed synchronize discharges ***(Browne and Holmes, 2001).***

Ictal termination:

Seizures do not cease as a result of neuronal exhaustion but due to loss of synchrony and active inhibition. Long lasting inhibitory postsynaptic potentials may be the result of both feed forward and feedback inhibitory influences. In the latter, feedback self-inhibition may operate in addition to lateral feed back inhibition ***(Okujava, 1996).***

Classification

The epilepsies had been designed as *primary* (idiopathic), secondary (symptomatic) or reactive ***(John et al., 2000).***

Table (1): Scheme for organizing epileptic conditions.

	With generalized seizures	**With partial (focal) seizures**
Primary (idiopathic) epilepsies Without structural lesions; benign; genetic	• Absence (petit mal) epilepsy • Juvenile absence epilepsy • Many generalized tonic-clonic seizures • Juvenile myoclonic epilepsy • Benign neonatal seizures	• Benign epilepsy with centrotemporal spikes (rolandic epilepsy) • Childhood epilepsy with occipital spikes
Secondary (symptomatic) epilepsies *With* anatomic or known biochemical lesions	• Infantile spasms • Lennox-Gastaut syndrome	• Temporal lobe (psychomotor) epilepsy • Epilepsies caused by gray matter heterotopias, polymicrogyria • Epilepsies caused by focal post-asphyxial gliosis
Conditions with ; reactive seizures Abnormal reaction of an otherwise normal \ brain to physiologic stress or transient epileptogenic insult	• Febrile seizures • Most toxic- and metabolic-induced seizures • Many isolated tonic-clonic seizures • Early post-traumatic seizures	• Partial seizures occur when conditions with reactive seizures are superimposed on transient or preexisting nonepileptogenic brain injury, as often seen with head trauma, hypernatremia, hypoglycemia

(Davis, 1989)

It is important to classify the type of seizures for several reasons first; the seizure type may provide a clue to the cause

of seizure disorder. In addition, precise delineations of the seizure may allow a firm basis for "making *"a* prognosis and choosing the most appropriate -treatment ***(Johnston, 2004)***

Table (2): International league against epilepsy revised classification of epilepsy.

(1) Localization-related (focal, local, partial) epilepsies and syndromes	
1.1	Idiopathic (with age-related onset)
	Benign childhood epilepsy with centrotemporal spikes
	Childhood epilepsy with occipital paroxysms
	Primary reading epilepsy
1.2.	Symptomatic
	Chronic progressive epilepsia partialis continua of childhood (Koshevnikoff syndrome)
	Syndromes characterized by seizures with specific modes of presentation
1.3	Cryptogenic (presumed symptomatic but etiology unknown)
(2) Generalized epilepsies and syndrome	
2.1	Idiopathic (with age-related onset, listed in order of age)
	Benign neonatal familial convulsions
	Benign neonatal convulsions
	Benign myoclonic epilepsy in infancy
	Childhood absence epilepsy
	Juvenile absence epilepsy
	Juvenile myoclonic epilepsy
	Epilepsy with grand mal (generalized tonic-clonic seizures) on awakeing
	Other generalized idiopathic epilepsies not defined above
	Epilepsies with seizures precipitated by specific models of activation (reflex and reading epilepsies)
2.2	Cryptogenic or symptomatic (in order of age)
	West's syndrome
	Lennox-Gastaut syndrome
	Epilepsy with myoclonic-astatic seizures
	Epilepsy with myoclonic absence

Table (2) Continued.

2.3	Symptomatic
2.3.1.	Non-specific etiology
	Early myoclonic encephalopathy
	Early infantile epileptic encephalopathy with suppression burst
	Other symptomatic generalized epilepsies not defined above
2.3.2.	Specific syndrome/etiology
	Cerebral malformations
	Inborn errors of metabolism including pyridoxine dependency and Disorders frequently presenting as progressive myoclonic epilepsy.
(3) Epilepsies and syndromes undetermined as to whether focal or generalized	
3.1	With both generalized and local seizures
	Neonatal seizures
	Severe myoclonic epilepsy in infancy
	Epilepsy with continuous spike waves during slow-wave sleep
	Acquired epileptic aphasia (Landau-Kleffner syndrome)
	Other undetermined epilepsies not defined above
3.2	Without unequivocal generalized or focal features
(4) Special syndromes	
4.1	Situation - related seizures
	Febrile convulsions
	Isolated seizures or isolated status epileptics
	Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, non-ketotic hyperglycemia Reflex epilepsy

(John, 2000).

I- Generalized Seizures:

1. Generalized tonic-colonic seizures (GTC): The most common type of generalized seizure is generalized tonic colonic. The clinical features of generalized tonic-colonic

seizures can be divided into five phases not all five phases occur in every person with every generalized seizure in the same patient. The first phase is characterized by a vague sense that a seizure is imminent, and it may last for hours or days.

The second phase is the immediate pre tonic-colonic phase, few myoclonic jerke or brief colonic brief clonic seizure may occur at this time. Some patients experience deviations of the head and eyes ***(Centrallas et al., 2002).***

The third phase (tonic) usually begins with a sudden tonic contraction of the axial musculature, accompanied by upward eye deviation and papillary dilatation. Tonic contraction of the limbs follows quickly. Involvement of the respiratory muscles produces a forced expiration of air, often resulting in an "epileptic cry" ***(Carl et al., 2005).***

The fourth phase (clonic) phase is gradual. Initially clonic activity is low amplitude; and in this stage the incontinence of urine and occasionally stool may occur with relaxation of the sphincter muscles ***(Carl et al., 2005).***

The fifth phase (postictal) period, the individual is generally unresponsive, but respiration returns. Muscle tone is generally decreased but is sometimes tonic with opisthotonos and trismus ***(Centrallas et al., 2002).***

2. Tonic seizures: Tonic seizures are brief seizures which last an average of 10 second but may persist for up to 1 minute. The onset of clinical features may be gradual or abrupt. A

myonclonic jerk occurs at the beginning, followed by a generalized tonic contraction ***(Centrallas et al., 2002).***

3. Atonic seizures: atonic seizures, commonly called drop attacks, occur abruptly and without warning and usually last 1-2 seconds. The main clinical feature is a sudden loss of tone, which may be limited to eye blinks or head drops but can involve the entire body. Loss of consciousness is very brief and often unnoticed ***(Carl et al., 2005).***

4. Generalized clonic seizures:

Generalized clonic seizures are rare and are usually seen in children with febrile illnesses. These seizures are characterized by an abrupt loss of consciousness with hypotonia or a generalized tonic spasm, followed by a series of myoclonic jerks. Motor involvement may be asymmetric, migratory, or focal. The interictal EEG in patients with clonic seizures reveals generalized spike or polyspike-wave discharges ***(Wheless, 1999)***

5- Absence seizures:

Simple (typical) absence (petit mal) seizures are characterized by a sudden cessation of motor activity or speech with a blank facial expression and flickering of eye lids. These seizure, which are un common before age 5 years, are more prevalence in girls, which are never associated with an aura, they rarely persist longer than 30 sec, and they are not associated with postictal state the ECG shows a typical 3/sec spike and generalized wave discharge ***(Johnston, 2004).***

A typical absence seizure generally exceed 10 seconds in duration, begin and end more gradually, and produce less marked alteration of consciousness. Tonic, a tonic, and myoclonic feature are commonly observed ***(Schaefer and Wyllie, 2003)***.

6. **Myoclonic seizures:**

Myoclonic seizures are single or repetitive, bilaterally synchronous and symmetric, rapid muscular contractions. Jerks are often restricted to facial and shoulder girdle muscles, although involvement of the trunk and limbs may occur. Consciousness is usually preserved. The EEG reveals generalized poly-spikes or spike-wave complexes, which may or may not be time-locked to the muscular contraction. Interictal findings vary from normal background rhythms with generalized epileptiform discharges to severe background abnormalities with multifocal spike discharges, depending on the etiology. Myoclonic seizures are commonly observed in neonates and children with idiopathic or symptomatic epilepsy ***(Wheless, 1999).***

II- Partial (Focal) Seizures:

A- Simple partial seizure: Result when the ictal discharge occurs in a limited and often circumscribed area of cortex, the epileptogenic focus. Almost any symptom or phenomenon can be the subjective (aura) or observable manifestation of a simple partial seizure, varying from elementary motor (Jacksonian seizures, adversive seizure)