Serum Insulin, Glucose ,Cortisol , and Neuropeptide Y Effect on BMI Of Epileptic children

thesis

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B y

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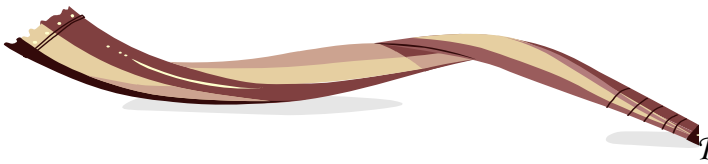

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Introduction

Epilepsy: is not uncommon problem in children, it has a prevalence of 3.5/1000 among Egyptian school children (**Elkhayat et al, 1994).**

Epilelpsy: is characterized by occasional (paroxysmal), excessive, and disorderly discharging of neurons that can be detected by clinical manifestations, elecroencephalographic(EEG)recording or both**(Thomas and Gregory,2003).**

Neruopeptide Y:(NPY) is a36amino acid peptide made by neurons throughout the brain and by other secretory cells of the body. Neroupeptide Y has been associated with number of physiologic processes in the brain, including the regulation of energy balance, memory and learning and epilepsy. In the hippo campus and neocortex, NPY is made by neurons that almost all express gamma amino butyric-acid.Many NPY containing interneurons also coexpress somatostatin.(**William et al.,2003)**

Insulin: is a hormone secreted from the beta-cells of the pancreatic islets in response to an elevation of blood glucose concentration (**Rosman,2005)**

Weight gain: is a common side effect of valproate treatment. The potential mechanisms of valproate-associated weight gain are not yet clear,decreased blood glucose level, impairment of b-oxidation of fatty acids, and increased insulin levels are some of the possible mechanisms(**Aydin et al .,2005)**

Cortisol : is adrenocorticoid hormone which is secreted under influence of adrenocorticotrophic hormone(ACTH) by adrenal cortex. Cortisol regulates the carbohydrates, proteins and lipids metabolism (**Asane,2007)**

The role of neuropeptide y,insulin and cortisol in valproate treated associated obesity is still controversial (**Aydin et al.,2005**)

Aim Of The Work

In this Study, we aim to estimate the level of serum insulin, glucose, cortisol and neuropeptide Y in epileptic children treated with valporoate and correlate their level with body mass index.

EPILEPSY

Definition of Epilepsy:

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

Age specific incidence:

The incidence is highest in the newborn period and higher in childhood than in later life ***(Moe and Benke, 2005).***

Epilepsy is higher in infants and in the elderly than dose of intermediate age, and is lower in higher socioeconomic classes ***(Sander, 2003).***

Sex incidence:

Men are 1-2.4 times more likely to have epilepsy than women ***(Sander, 1995).***

El-Khayat et al., (1994), reported that primary epileptic male: female ratio of about (1.4:1). This was nearly similar to that reported by ***Levados et al., (1992)*** which was (1.25:1).

Incidence by seizure type:

Epilepsy, manifested by generalized onset seizures, accounts for most of the newly diagnosed cases of epilepsy in the first five years of life ***(Hauser, 1995).*** After that age, epilepsy manifested by partial

seizures accounts for 50% or more of the newly identified convulsive disorders ***(Hauser et al., 1993).***

Prevalence:

A number of studies have been reported allowing comparison of prevalence rate of epilepsy among population, the British national child development study reported prevalence rate for epilepsy of 7, 11, 5 and 6 per 1000 at age of 7, 11, 16 and 23 years ***(Kurtz and Tookey, 1998).***

In a study in two central Oklahoma cities in U.S.A.,(***Cowan et al. 1989)*** reported a prevalence rate of 4.71 per 100 children from birth till the age of 19 years. This result is comparable to that reported by (***Liu et al. 1995)*** who studied a population of 100, 589 children in China and reported a prevalence rate of 4.5 in 1000 (58% males and 42% females).

In Egypt,(***Mekky 1981)*** studying the epidemiology of epilepsy demonstrated a prevalence of 4.1 per 1000 population, the highest prevalence was in the age group 10-19 years reaching 7.4 per 1000. on the other hand,(***El-Afify 1981)*** who studied epilepsy in El-Sahel teaching hospital reported a prevalence rate of 9.87 per 1000 population, whereas ***(El-Khayat et al. 1994)***, studying the prevalence of epilepsy in children 6-9 years, reported a prevalence rate of 3.5 per 1000. (***Massoud 1997)***, in his study on school children of 195 schools in Cairo, reported even a lower overall prevalence of 1.91/1000.

Etiology of Seizures:

Although the majority of children with seizures have idiopathic epilepsies yet, a significant minority have identifiable etiologies (Table 1).***Table (1):*** *Causes of seizures*

Perinatal condition	**Neurocutaneous syndromes**
Cerebral malformation	Tuberous sclerosis
Intrauterine infection	Neurofibromatosis
Hypoxic ishaemic encephalopathy*	Sturge –Weber syndrome
Trauma	Klippel-Trenaunay-Weber syndrome

Hemorrhage*	Linear sebaceous nerves
	Incontinentia pigmenti
Infections	**System disorders**
Encephalitis*	Vasculitis (CNS or systemic
Meningitis*	Systemic lupus erythematosis
Brain abscess	Hypertensive encephalopathy
Metabolic conditions	Renal failure
Hypoglycemia*	Hepatic encephalopathy
Hypocalcemia	Cerebral venous thrombosis
Hyponatremia	
Hypomagnesemia	**Others**
Hypernatremia	Trauma*
Storage diseases	Tumour
Reye syndrome	Febrile*
Degenerative disorders	Idiopathic*
Porphyria	Familial
Pyridoxine dependency and deficiency	
Poisoning	
Lead	
Cocaine	
Drugs toxicity	
Drug withdrawal	

* *Common*

(Lewis, 2006)

Genetics of Childhood 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 now is 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 heterogenecity.

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 ***(Lieven 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 a 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 arresting 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 -5o to-80Mv.ion leaks across the membrane occur moving from high concentration to low concentration: Na+ leaks in and 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 cell 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(GABA) 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. Neurotransmitters 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 (guany 1 nucleotide – binding 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 2nd messenger systems include