Introduction

Epilepsy is one of the most common and challenging neurological disorders affecting children ***(Jarrar and Buchalter, 2003)***.

The cumulative lifetime incidence of epilepsy is now considered to be 3% where more than half of the cases begin in childhood ***(Johnston, 2004)***.

An epileptic seizure is the result of temporary physiologic dysfunction of the brain caused by a self-limited abnormal, hypersynchronous electrical discharge of cortical neurons ***(Carl et al., 2005)***.

Omega-3 fatty acids (Polyunsaturated Fatty Acids) or n-3 PUFAs) are essential for normal brain development and that a deficiency in these fatty acids can contribute to the emergence of neurologic dysfunction ***(Schlanger et al., 2002)***.

Nutrition is likely to be one of the factors contributing to seizures and, in particular, deficiency in omega-3 fatty acids might be an important factor. Omega-3 fatty acids have important roles in determining the structural and functional properties of neuronal

membranes, affecting membrane functions such as electrical signaling, receptor sensitivity, and neurotransmitter release ***(Schlanger et al., 2002)***.

Recent studies have shown that n-3 PUFAs can raise the threshold of epileptic seizures, furthermore, a substantial improvement in the frequency and strength of seizures has been noticed when epileptic patients were put on PUFA supplementation ***(Schlanger et al., 2002)***.

Aim of the Work

The aim of this work is to determine the levels of serum PUFAs in children with idiopathic intractable epilepsy on more than one antiepileptic drug who are poorly controlled.

Patients demonstrating decreased levels of PUFAs (compared to controls) will receive oral supplementation of omega-3 fatty acids for 6 months and their serum levels of PUFAs will be reassessed and compared to controls again. Seizure frequency and severity will be assessed before and after supplementation.

Patients demonstrating equal or increased levels of PUFAs (compared to controls) will receive oral supplementation of omega-3 fatty acids for 6 months and their serum levels of PUFAs will not be reassessed, but seizure frequency and severity will be reassessed.

Epilepsy

Definition:

The word “epilepsy” is derived from a Greek word which means to be seized by forces from without, it refers to the old magic concept that diseases were "attacks or seizures" by Gods and demons ***(Aicardi, 1986)***.

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

A seizure can be defined as a sudden, transient disturbance of brain function manifested by involuntary motor, sensory, autonomic or psychic phenomena, alone or in combination, often accompanied by alteration or loss of consciousness ***(Moe and Benke, 2005)***.

Epidemiology of epilepsy:

Epilepsy is a highly prevalent disease, affecting 0.5-1.5% of the world's population ***(Hauser, 1995)***, the overall prevalence of the epilepsies in childhood and adolescence is 4-6 per 100 ***(Cowan et al., 1989)***.

The incidence of epilepsy in developing countries is more than 100 in 100.000 of normal population. This high rate in developing countries is mainly due to acute infections, parasitic infestations and poor postnatal care ***(Jallon, 2002)***.

In Egypt, ***El-Khayat et al. (1994)***, studied the prevalence of epilepsy in primary school children and reported a prevalence rate of 3.5/1000 while ***Massoud, (1997)***, in his study on children of 195 primary schools in Cairo, reported even a lower overall prevalence (of 1.9/1000).

Generalized seizures and epilepsy syndrome types are more prevalent in children 0-6 years of age, while partial/localization types are more prevalent in children aged 6-15 years ***(Eriksson and Koivikko, 1999)***.

Pathophysiology:

Basic mechanisms of epileptogenesis:

From a neurophysiological point of view, an epileptic seizure has been defined as an alteration of central nervous system function resulting from spontaneous electrical discharge in a diseased neuronal population of cortical grey matter or the brain stem ***(Menkes, 2000)***.

Mechanism of neuronal excitation:

Excitable membrane and microenvironment:

The resting membrane potential of neuron is negative inside with a value of 60-80mv, which is maintained by Na-K pump ***(Ganong, 2000)***. Under resting condition, there is intracellular deficiency of Na^+, Ca^{++} and Cl^-.

Opening of any channel that permits their passage will result in their influx and membrane depolarization in cases of Na^+ and, Ca^{++}, and hyper polarization in cases of Cl^-. On the other hand, there is excess intracellular K^+, and opening of K^+ channel will result in membrane hyperpolarization ***(Menkes and Sanker, 2000)***.

Maintenance of the potential across the membrane requires energy ATP-dependent pump, thus a disturbance of energy production can result in failure of Na-K pump, as in case of hypoxia, ischemia and hypoglycemia ***(Leppert, 2000)***.

Extracellular ionic concentrations also contribute to neuronal excitability. Increased extra-cellular K^+, reducing K^+ hyperpolarizing currents will cause membrane depolarization.

Mg^{++} ions, on the other hand, block Ca entry to cells at resting membrane potential. Thus decreased extracellular Mg^{++} will enhance membrane excitability ***(Burgess and Nobels, 2000)***.

The facilitatory factors of seizure activity:

Glutamate and *aspartate* are the excitatory neurotransmitters. They produce membrane depo-larization with a rapid time course by inducing Ca^{2+} currents, and are the most important excitatory neurotransmitters in the CNS ***(Bray et al., 1994)***.

Glutamate receptor agonist such as N-methyl-D-aspartate produce epileptic foci, moreover, accumulation of N-methyl-D-aspartate in the CNS induces epileptic seizures ***(Kazuhiro et al., 2001)***.

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)***.

The inhibitory factors of seizure activity:

Gamma Amino Butyric Acid (GABA) is the major inhibitory neurotransmitter in the CNS, which can open

either Cl^- or K^+ channels. Glycine, which produces inhibitory effect on postsynaptic membrane by opening Cl^- channels, is mainly limited to the spinal cord and brain stem. Taurine is reported to have an inhibitory property ***(Olsen and Avoli, 1997)***.

Epilepsy may result from a genetic lesion that produces a decrease in GABA inhibition. Seizures resulting from pyridoxine deficiency are postulated to involve a reduction in brain GABA through decreasing the activity of its synaptic enzyme: Glutamic Acid Decarboxylase (GAD). A disturbance in binding of the critical cofactor PLP (Pyridoxal-5-phosphate) would thus be expected to cause a relative decrease of GABA ***(Bernard et al., 2000)***.

Adenosine is another potent inhibitor of cortical neurons, acting primarily by depressing spontaneous neuronal firing or synaptic transmission through its inhibition of the presynaptic release of excitatory neurotransmitters ***(Chin, 1989)***.

Etiology:

Genetic aspects of epilepsy:

Genetic factors influence the development of seizures, although a definite chromosomal or a single-gene

abnormality can be demonstrated only in 1% of epileptic patients ***(Bazil et al., 2005)***.

For most types of seizures, polygenic or multifactorial factors exist. Only a small number of seizure disorders are inherited as autosomal, or very rarely, X-linked traits. Siblings and offsprings of persons with seizures disorders have an increased risk to develop seizures; the risk is approximately 1-10% ***(Margretta and Rebecca, 1996)***.

Causes of epilepsy:

Epilepsy has many causes and indeed almost all grey matter diseases can result in seizures and the most important factors influencing the range of causes is age ***(Schmidt and Sorvon, 1996)***.

In about 60% of diagnosed epileptics, no reasonable cause for the seizure is found, and the condition is referred to as idiopathic ***(Nordli et al., 2003)***. Many systemic disorders and almost all local pathological processes that involve the brain can result in epilepsy; this is demonstrated in (Figure 1) ***(Hauser et al., 1993)***.

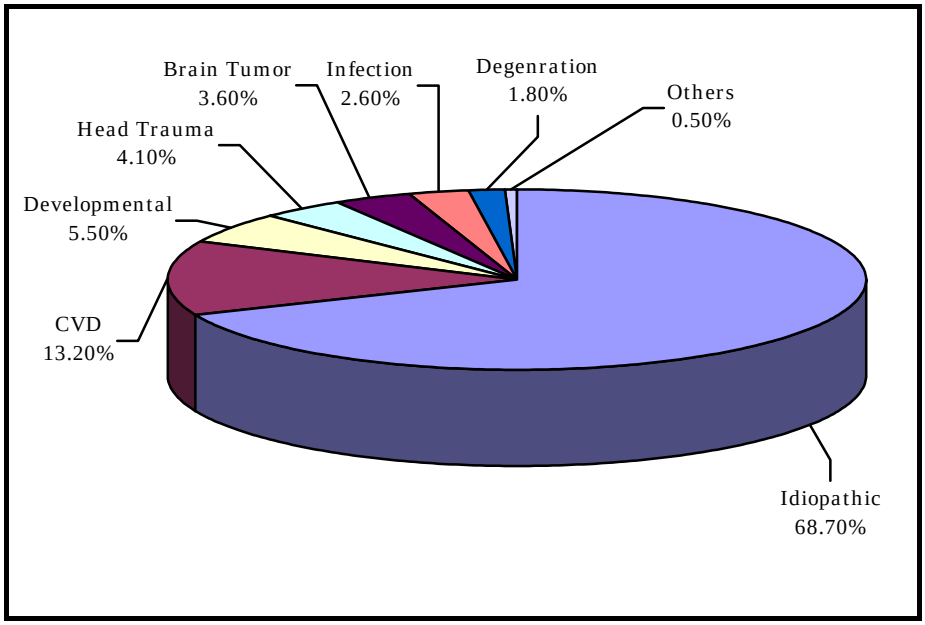

Fig. (1): **Etiology of epilepsy** ***(Hauser et al., 1993)***

Most etiologic factors associated with epileptic seizures are included in table (1).

Table (1): **Etiology of seizures**

• **Perinatal conditions:**	• **Neurocutaneous syndromes:**
Cerebral malformation. Intrauterine infection. Hypoxia-ischemia. Trauma. Hemorrhage.	Tuberous sclerosis. Neurofibromatosis. Sturge-weber syndrome. Incontinentia pigmenti.
• **Infections:**	• **Systemic disorders:**
Encephalitis. Meningitis. Brain abscess.	Vasculitis. SLE. Hypertensive encephalopathy. Renal failure. Hepatic encephalopathy.
• **Metabolic conditions:**	• **Others:**
Hypoglycemia. Hypocalcemia. Hypomagnesemia Hyponatremia. Hypernatremia.	Trauma. Tumor. Febrile. Familial. Idiopathic.
• **Poisoning:**	
Lead. Cocaine. Drugs: Drug withdrawal.	

(Bergman and Painter, 2000)

Many drugs are also associated with epileptic seizures; this can be demonstrated in table (2).

Table (2): Drugs associated with epileptic seizures

• **Anaesthetics**	• **Antidepressants**
Ether. Halothane. Ketamine.	Amitryptiline. Impiramine. Mianserin.
• **Analgesics**	• **Antipsychotics.**
Pethidine. Pentazocine.	Chlorpromazine. Lithium.
• **Antibiotics**	• **Bronchodilators**
Penicillin, ampicillin. Carbencillin. Isoniazide. Nalidixic acid. Oxacillin. Metronidazole.	Aminophyline. Theophylline.
• **Others**	• **Antineoplastic agents**
Insulin. Antihistamines. Baclofen. Folate. Interferon.	Vincristine. Chlorambucil. Methotrexate.

(Marshall and Mayer, 1997)

Also children with complicated prolonged febrile convulsions are thought to develop complex partial seizures in later life ***(Jiang et al., 1999)***.

The spectrum of epileptic seizures and syndromes:

The International League Against Epilepsy (ILAE) proposed a classification of epileptic seizures in 1969, which was revised in 1981 ***(Commission on Classification and Terminology of the ILAE, 1981)***. In 1985, this was supplemented by a classification of epilepsies and epileptic syndromes ***(Dreifuss et al., 1985)***. And this classification was also revised ***(Roger et al., 1989)***.

Table (3): ILAE classification of epileptic seizures

I. Partial (focal) seizures:
- ***A. Simple partial seizures (consciousness not impaired):***
  1. With motor signs (including Jacksonian, versive, and postural).
  2. With sensory symptoms (including visual, somatosensory, auditory, olfactory, gustatory, and vertiginous).
  3. With psychic symptoms (including dysphasia, dysmensic, hallucinatory, and affective changes).
  4. With autonomic symptoms (including epigastric sensation, pallor, flushing, pupillary changes).
- ***B. Complex partial seizures (consciousness impaired):***
  1. Simple partial onset followed by impaired consciousness.
  2. With impairment of consciousness at onset.
  3. With automatisms.
- ***C. Partial seizures evolving to secondarily generalized seizures.***

II. Generalized seizures of nonfocal origin (convulsive or nonconculsive):
- ***A. Absence seizures:***
  1. With impaired consciousness only.
  2. With one or more of the following: atonic components, tonic components, automatisms, autonomic components.
- ***B. Myoclonic seizures:***
  Myocolonic jerks (Single or multiple).
- ***C. Tonic-clonic seizures*** (may include tonic-clonic and clonic seizures).
- ***D. Tonic seizures.***
- ***E. Atonic seizures.***

III. Unclassified epileptic seizures.

ILAE Commission report, (1981)

I. Partial seizures:

Partial seizures are those in which the first clinical symptoms indicate initial activation of a system of neurons limited to a part of one cerebral hemisphere.

They account for a large proportion of childhood seizures, up to 40% in some series ***(Johnston, 2004)***.

A. Simple partial seizures (SPS):

These are focal seizures in which there is no alteration of consciousness, where the ictal discharge occurs in a limited area of the cerebral cortex, almost any symptoms can be the subjective aura, observable manifestation of simple partial seizures varying from elementary, motor and sensory disturbances to emotional, psychoillusionary or dysmensic phenomena ***(Bazil et al., 2005)***.

The average seizures persist for 10-20sec. The distinguishing characteristic of the SPS is that the patients remain conscious during the seizures. Furthermore, no postictal phenomenon follows the event ***(Johnston, 2004)***.

B. Complex partial seizures (CPS):

CPS arises in the cortex most often the temporal lobe, but also can originate from frontal or parietal lobe ***(Fenichel, 2005)***.

CPS, as emphasized by the international classification of seizures, must include some impairment of consciousness ***(Kotagal, 1990)***. Complex partial seizures mostly last for 1 to 2 minutes and rarely less than 30 seconds. Less than 30% of children report an aura. It is usually a non-descript unpleasant feeling, but also may be a stereotyped auditory hallucination or abdominal