INTRODUCTION

The ketogenic diet was first introduced in the 1920s from the observation that starvation resulted in a decrease of seizure frequency ***(Wheless, 2008).***

The ketogenic diet includes 80% fat, 15% protein, and 5% carbohydrate; the ratio of fat to carbohydrate plus protein ranges from 2:1 to 4:1, with higher ratios seen as more restrictive but more effective ***(Freeman et al., 2000; Seo et al., 2007).***

There is no longer any doubt that the KD is effective in ameliorating seizures in patients, especially children, with medically refractory epilepsy ***(Vining, 1999; Neal et al., 2008; Freeman et al., 2009)*** which is failure to control seizures despite a trial of two or three drugs that are suitable for the type of epilepsy and have been appropriately prescribed at maximum tolerated doses ***(Berg, 2004).***

While the mechanisms underlying its anticonvulsant effects remain incompletely understood ***(Hartman et al., 2007; Bough and Stafstrom, 2010; Rho and Stafstrom, 2011),*** There have been several hypotheses about the mechanisms of antiepileptic effects by the ketogenic diet ***(Hartman et al., 2007).***

The early hypotheses regarding the ketogenic diet activities were focused on the concepts of acidosis and increased ketone concentrations ***(Masino et al., 2012)***

Recently, some studies have reviewed these mechanisms, emphasizing that the beneficial effects of the KD also involve caloric restriction ,in addition to the increased levels of uncoupling protein (UCPs) and the decreased production of reactive oxygen species (ROS) ***(Yuen et al., 2014).***

Patients on the diet become more alert and exhibit considerable improvements in attention, comprehension, activity levels, and endurance ***(Nordli, 2002).***

Most of the side effects from the ketogenic diet are related to energy and nutrient deficiencies. Lack of protein, carbohydrates, and other nutrients can result in lack of weight gain and growth inhibition, especially at a young age. Inadequate calcium intake can further impair bone mineralization in children already at risk of osteopenia due to antiseizure therapy. Lack of fibre in the diet causes constipation. Acidosis is also commonly observed. Less common are kidney stones and hyperlipidemia ***(Vining, 2002).***

Aim of the Work

Assessment of effect of using Modified Atkins diet (MAD) as line of therapy on quality of life of patients with intractable epilepsy as well as assessment of efficiency and tolerability of the diet.

EPILEPSY

It is a common chronic neurological disorder characterized by recurrent unprovoked seizures ***(Blume et al., 2001),*** these seizures are transient signs of abnormal excessive or synchronous neuronal activity in the brain ***(Fisher et al., 2005).*** These episodes can vary from brief and nearly undetectable to long periods of vigorous shaking.

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).***

Incidence:

About 50 million people worldwide have epilepsy, with almost 90% of these people being in developing countries ***(National Society for Epilepsy, 2009).***

Age specific incidence:

Incidence rates are highest among young children and the elderly ***(Bazil et al., 2005).*** Also Moe and Benke reported that it is highest in the newborn period and higher in childhood than in later life ***(Moe and Benke, 2005).***

Sex incidence:

In the systematic review of incidence studies, the median annual incidence of epilepsy was 50.7 per 100,000 for males and 46.2 per 100,000 for females ***(Kotsopoulos et al., 2002)***, another study found almost an equal sex incidence ***(Freitag et al., 2001).***

Prevalence:

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

Pathophysiology:

Two sets of changes can determine the epileptogenic properties of neuronal tissue. Abnormal neuronal excitability is believed to occur as a result of disruption of depolarization and repolarization mechanisms of the cell (this is termed the excitability of neuronal tissue). Aberrant neuronal networks that develop abnormal synchronization of a group of neurons can result in the development and propagation of an epileptic seizure (this is termed the synchronization of neuronal tissue ***(Engel et al., 1989).***

Neurons are influenced by synaptic and non synaptic interconnections. Neurochemical transmission between neurons

involves a number of steps that can be selectively altered to affect neuronal excitability, these steps result in release of neurotransmitters into the synaptic cleft and postsynaptic membrane, result in excitatory or inhibitory postsynaptic potentials via calcium and other second messengers, the transmitters are deactivated by enzymes, by reuptake into axon terminals or by uptake by glia. The primary excitatory neurotransmitters in CNS are glutamate and aspartate, while the primary inhibitory neurotransmitters are gamma-amino butyric acid (GABA) and glycine ***(Dudek et al., 2010).***

Genetic aspect of epilepsy:

Genetic factors play a role in several epilepsy syndromes starting in the first year of life. Molecular genetic studies have identified causative genes and loci for a number of these early-onset epilepsies, This knowledge has consequences for clinical practice as it opens new perspectives for genetic testing, improving early diagnosis and facilitating genetic counseling ***(Deprez et al., 2009).***

There are several indicators of a genetic etiology for idiopathic epilepsy. These include an increased familial incidence and frequent clinical concordance which are emphasized by the results of several studies ***(Gutierrez-Delicado and Serratosa, 2004).***

For most types of seizures, polygenic or multifactorial factors exist. Only a small number of seizures disorders are

inherited as autosomal, or very rarely X linked traits, siblings and off springs of persons with seizure disorders have an increased risk is approximately 1-10% ***(Seashore and Wappner et al., 1996).***

Different mutations in genes that control the excitability of neurons have been described in childhood epilepsies ***(Lagae, 2008).***

Only a few "monogenic epilepsies" were clearly identifies, but the underlying genetic mechanisms involved were found to affect major pathophysiological pathways in the brain. The large majority of the genes involved are regulating excitation and inhibition at the neuronal and the synaptic levels. The major players involved are the potassium, sodium, GABA receptor and chloride channelopathies ***(Heron and Scheffer et al., 2007).***

Etiology:

Although the majority of children with seizures have idiopathic epilepsies yet, a significant minority have identifiable etiologies ***(Lewis, 2006).***

Epilepsy has a wide range of causes and indeed almost all grey matter diseases can result in seizures and the most important factor influencing the range of causes is age ***(Kobayashi et al., 2006).***

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

Perinatal conditions Cerebral malformation Intrauterine infection Hypoxic ischemic encephalopathy Trauma Hemorrhage	**Neurocutanous syndromes** Tuberous sclerosis Neurofibromatosis Sturge-Weber syndrome Klippel-Trenaunay-Weber syndrome Linear sebaceous nevus Incontinentia pigmenti
Infection Encephalitis Meningitis Brain abscess	**Systemic disorders** Vasculitis (CNS or systemic) Systemic lupus erythematosis Hypertensive encephalopathy Renal failure Hepatic encephalopathy Cerebral venous thrombosis
Metabolic conditions Hypoglycemia Hypocalcaemia Hyponatremia Hypomagnesemia Hypernatremia Storage disease Reye syndrome Degenerative disorders Porphyria Pyridoxine dependency and deficiency	**Others** Trauma Tumor Febrile Idiopathic Familial
Poisoning Lead Cocaine Drugs toxicity Drug withdrawal	

(Lewis, 2006)

The possibility that febrile convulsions in early childhood (younger than 5 years) are etiologic factors in human temporal lobe epilepsy (TLE) has been proposed by many investigators; particularly children with complicated prolonged febrile convulsions are thought to develop complex partial seizures in later life ***(Jiang et al., 1999).***

Classification:

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 affirm basis for making a prognosis and choosing the most appropriate treatment ***(Johnston, 2004).***

The International League against Epilepsy classification ***(ILAE, 1981),*** has defined the seizure type on basis of clinical and EEG finding into; partial and generalized seizures ***(Engel, 2006).***

Table (2): Classification of seizure types by International League aginst Epilepsy

I- Partial Seizures:
A. Simple partial (focal) seizures: (consciousness retained) - Motor - Sensory - Autonomic - Psychic
B. Complex partial seizures (CPS): (consciousness impaired) - Simple partial followed by impaired consciousness
C. Partial seizures evolving to secondarily generalized seizures.
II- Generalized seizures:
A. Absence seizures: B. Generalized tonic-clonic seizures (GTC). C. Tonic seizures: D. Clonic seizures: E. Myoclonic seizures: F. Atonic seizures:
III- Unclassified seizures.

(Johnston, 2004)

ILAE classification of epilepsy and epilepsy syndromes:

In recognition of the limitations of a seizure type-classification, the ILAE commission on classification and terminology proposed a new compound scheme. This was a more ambitious attempt to classify epilepsies, not simply on the basis of the seizure type but also to incorporate anatomical, EEG, etiological seizure type and precipitation and other syndromic features ***(Commission on classification and terminology of ILAE, 1989).***

I. Idiopathic epilepsy:

The term primary or idiopathic epilepsy implies that, with present knowledge, no structural or biochemical causes for the recurrent seizures can be found. This type tends to be self-limited and responds readily to antiepileptic drugs. Genetic factors are important in this type and its manifestations are typically age-related ***(Engel, 2001 and Fisher et al., 2005).***

II. Symptomatic epilepsy:

Symptomatic epilepsy occurs in the setting of a specific brain insult and it is thought to be a cause of tendency to recurrent seizures ***(Engel, 2001).***

III. Cryptogenic epilepsy:

Underlying cause seems probable but has not (yet) been definitively identified (presumed symptomatic) ***(Engel, 2001 and Pedley et al., 2005).***

Table (3): ILAE classification of epilepsy and epilepsy syndromes:

1. Generalized: **Idiopathic generalized epilepsies with age-related onset (in order of age):** Benign neonatal familial convulsion. Benign neonatal convulsion. Childhood myoclonic epilepsy in infancy. Childhood absence epilepsy. Juvenile absence epilepsy. Epilepsy with generalized tonic-clonic seizure on a weaking. Other idiopathic generalized epilepsies not defined above. Epilepsies with seizures precipitated by specific modes of activation.
Cryptogenic generalized epilepsies (in order of age): West syndrome. Lennox-Gastaut syndrome. Epilepsy with myoclonic-a static seizure. Epilepsies with myoclonic absences.
Symptomatic generalized Epilepsies: Non specific etiology: Early myoclonic encephalopathies. Early infantile encephalopathy with burst suppression. Other symptomatic epilepsies not defined above. Specific syndromes: Epilepsies in other disease states.
2. Localization-related: **Localization-related epilepsies-idiopathic with age related onset:** Benign epilepsy with Centro-temporal spikes. Childhood epilepsy with occipital paroxysms. Primary reading epilepsy. **Localization-related epilepsies-cryptogenic.** **Localization-related epilepsies-symptogenic.** Epilepsia partialis continua. Familial characterized by specific modes of precipitation. Temporal lobe epilepsies. Frontal lobe epilepsies. Parietal lobe epilepsies.
3. Epilepsies and syndromes undetermined as to whether focal or generalized: With both generalized and focal seizure: Neonatal seizures. Severe myoclonic epilepsy in infancy. Electrical status epilepticus in slow-wave sleep. Acquired epileptic aphasia.
4. Special syndromes: Febrile convulsion. Seizures occurring only when there is an acute metabolic or toxic event caused by factors such as alcohol, drugs, eclampsia, non-ketotic hyperglycemia.

(Commission on classification and terminology of ILAE, 1989)

Diagnosis:

The diagnosis of epilepsy is fundamentally a clinical judgment made on the basis of a clinical history and the accuracy of the diagnosis depends on the skill and experience of the physician and the quality and reliability of the information provided by witnesses ***(Radhakrishnan, 2009).***

So, there are four separate factors important for accurate diagnosis discussed in the following four questions ***(Simkiss et al., 2001)*****:**

- Is this epilepsy or not? Important differential diagnosis includes syncope (reflex, cardiac or postural) night tremors, breath holdings attacks, movements' disorders and migraine.
- If this is epilepsy, what seizures types does the child have? These are classified by ILAE.
- If this is epilepsy, does the constellation of seizure types and other clues constitute an epilepsy syndrome?
- If this is epilepsy, what is its etiology?

Accurate diagnosis leads directly to proper treatment and formulation of rational plan of management ***(Bazil et al., 2005).***

A. History:

The transient occurrence of altered awareness, abnormal behavior, or involuntary movements suggests a diagnosis of epilepsy. Because epileptic seizures are rarely observed by a physician, the diagnosis is typically based on historical information supplemented by selected tests. A careful history is the single most important element in diagnosis, with a focus on details of the episode and whether there is any history of previous spells that may point to a diagnosis of epilepsy. When patients have limited or no recall of events, witnesses should be queried about details of the episode. The differential diagnosis varies according to the patient's age and symptoms ***(French and Pedley, 2008).***

The history for etiology should include questions regarding family history of epilepsy, head trauma, birth complications, febrile convulsions, middle ear and sinus infections or drug abuse and symptoms of malignancy.

The history for precipitation factors should include factors such as fever, sleep deprivation, hyperventilation, flickering lights or television ***(Pedley et al., 2005)***.

B. Physical examination:

It should be done to discover evidence of past or recent head trauma, infections of the ears and sinuses, congenital abnormalities, focal or diffuse neurological abnormalities or drug abuse and signs of malignancy ***(Camfield et al., 2002)***.

C. Investigations:

The investigations of seizures depend on many factors including the age of the patient, the type and frequency of the seizures and the presence or absence of neurological findings and constitutional symptoms ***(Johnston, 2004).***

They may be grouped into:

- **Functional:**

1) Electroencephalography (EEG):

EEG plays a central role in diagnosis and management of patients with seizures disorders, because it is convenient and relatively.

Inexpensive way to demonstrate the physiological manifestations of abnormal cortical excitability that underlie epilepsy. Normal EEG does not exclude epilepsy as around 10% of patients with epilepsy never show epileptiform discharge ***(Smith et al., 2005).***

Because epilepsy is fundamentally a physiologic disturbance of brain function, the EEG is the most important laboratory test in evaluating children with seizures ***(Nordli et al., 2003).***

Ictal EEG:

The EEG is invariably abnormal if recorded during the ictus. Normal ictal EEG is strong evidence that the seizure is non epileptic ***(Weisberg et al., 1996).***

Interictal EEG*:*

Because epilepsy is intermittent and unpredictable disorder most EEGs in patients with seizures are obtained between rather than during attacks ***(Menkes et al., 2000)***.

A normal EEG does not exclude the diagnosis of epilepsy because interictal recording is normal in approximately 40% of patients **(Johnson et al., 2004)**.

Ambulatory EEG*:*

A portable cassette recorder is used to monitor the EEG continuously over prolonged periods. This allows detection of infrequent interictal localized discharges ***(Schomer et al., 2006).***

Video EEG telemetry*:*

This provides long term monitoring of EEG and time locked video for the patient in a dedicated recording room ***(Cascino et al., 2001).*** This technique is extremely helpful in the classification of seizures while recording alteration in the level of consciousness and presence of clinical signs ***(Johnson et al., 2004).***