INTRODUCTION

Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition ***(David, 2014).***

A task force of the International League against Epilepsy proposed that drug-resistant be defined as the failure of adequate trials of two tolerated, appropriately chosen and administered antiepileptic drugs (whether as monotherapy or in combination) to achieve seizure freedom. They also recommended replacing the term "intractable" with "drug-resistant" epilepsy (DRE) ***(Kwan, 2010)***.

The ketogenic diet (KD) is a well-established treatment for drug-resistant childhood epilepsy with expanding indications, especially in the neurometabolic field. Although the underlying mechanisms of action remain partly unclear, recent work indicates that several mechanisms of action may exist for the ketogenic diet, including the disruption of glutamatergic synaptic transmission, the inhibition of glycolysis and the activation of ATP-sensitive potassium channels ***(Lutas and Yellen, 2013).***

KD has been used since the first reports of beneficial effects on seizure control in the 1920s ***(Freeman et al., 2009).***

There are several reasons underlying the elevated risk of developing renal calculi in patients on the ketogenic diet ***(Furth et al., 2000).***

First, hypercalciuria can develop due to chronic metabolic acidosis. This metabolic acidosis not only decreases calcium reabsorption in the renal tubules, thus increasing urinary calcium excretion, but also increases bone demineralization because bone phosphate acts as an acid buffer ***(Furth et al., 2000).***

Second, children on a ketogenic diet show hypocitraturia. Citrate normally binds urine calcium, lowering its concentration, acting as an inhibitor of calcium crystallization. Acidosis induces proximal tubules to both increase citrate absorption and decreases its excretion. As a result, acidosis not only reduces urinary citrate excretion but also increases urinary calcium excretion, aggravating renal stone formation ***(Kielb et al., 2000).***

Third, chronic acidosis persistently causes low urinary pH, which facilitates uric acid crystal formation due to lowered uric acid solubility. These crystals can act as a nidus for calcium stone formation. Lastly, dehydration may be the most significant factor in calculus formation in children on the ketogenic diet, primarily because ketosis has been shown to interfere with the normal thirst mechanism ***(Sampath et al., 2007).***

AIM OF THE WORK

This study aims to evaluate risk factors for development of renal stone in drug- resistant epileptic children on the ketogenic diet.

Chapter 1

EPILEPSY

Definition:

Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition ***(David, 2014).***

Incidence:

The annual incidence of epilepsy is 5–7 per 10,000/yr. The highest incidence of epilepsy occurs in patients less than 1 yr and in the elderly ***(Anyanwu and Motamedi, 2012).***

Prevalance:

The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or the need for treatment) at a given time is between 4 and 10 per 1,000 people. However, some studies in developing countries suggest that the proportion is between 6 and 10 per 1,000. Around 50 million people in the world have epilepsy. In developed countries, annual new cases are between 40 and 70 per 100,000 people in the general population. In developing countries, this figure is often close to twice as high due to the higher risk of experiencing conditions that can lead to permanent brain damage. Close to 90% of epilepsy cases worldwide are found in developing regions ***(WHO, 2009).***

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 of1.9/1000.

Genetic and developmental Mechanisms:

The recent advances in genetics have made limited inroads into understanding the genetic basis of epilepsy. The most impressive findings have been made in relation to the symptomatic epilepsies of metabolic origin, and the defective gene causing almost all of the single-gene metabolic– neurologic disorders has now been identified. Fifteen genes have also been identified coding for ‘‘pure’’ epilepsies, but despite intensive efforts, the genetic bases of the great majority of idiopathic epilepsies remain largely obscure. The reason is likely to be that idiopathic epilepsy is caused by more complex genetic or developmental processes, and large epistatic and epigenetic influences will be present ***(Shorvon et al., 2011)***.

The current emphasis on finding causal single nucleotide polymorphisms (SNPs) seems naive, and untangling the epigenetic and epistatic mechanisms will pose a formidable challenge, yet these mechanisms probably hold the key to the (missing heritability) of epilepsy ***(Mastrangelo and Leuzzi, 2012).***

Other genetic approaches may also help, and these include studies of such mechanisms as copy number variation, genomic imprinting, chromosomal imbalance, X inactivation, and mitochondrial mechanisms. How the category of ‘‘idiopathic’’ epilepsy will appear in the future after these further research efforts have come to fruition is unclear. It should also be noted that many genetic influences are not ‘‘all or none’’ but confer susceptibility. Where the line is drawn in these cases between a genetic or cryptogenic categorization is arbitrary ***(Battaglia et al., 2008).***

Table (1): Mendelian idiopathic epilepsy syndromes with genes identified by positional cloning:

Epilepsy syndrome	Gene	Chromosomal location	References
Benign familial neonatal seizures	KCNQ2 KCNQ3	20q13 8q24	***Singh et al., 1998.*** ***Charlier et al, 1998.***
Benign familial neonatal–infantile seizures	SCN2A*	2q24	***Heron et al., 2002***
Childhood absence epilepsy with febrile seizures	GABRG2*	5q31	***Kananura et al., 2002***
Autosomal dominant juvenile myoclonic epilepsy	GABRA1 EFHC1	5q34 6p12	***Cossette et al., 2002*** ***Suzuki et al., 2004***
Autosomal dominant idiopathic generalized epilepsy	CLCN2	3q26	***Singh et al., 1998***
Autosomal dominant nocturnal frontal lobe epilepsy	CHRNA4 CHRNB2	20q13 1q21	***Steinlein et al., 1995*** ***De Fusco et al., 2000***
Autosomal dominant partial epilepsy with auditory features	LGI1	10q24	***Morante-Redolat et al., 2002***
Generalized epilepsy with febrile seizures plus. (GEFS+)	SCN1B SCN1Ab** SCN2Aa* GABRG2*	19q13 2q24 2q24 5q31	***Wallace et al., 1998*** ***Sugawara et al., 2001*** ***Sugawara et al, 2001*** ***Harkin et al., 2002***

**Mutations identified in more than one epilepsy syndrome.*

*** De novo mutations also identified in severe myoclonic epilepsy of infancy.*

(Ottman, 2005)

Etiology:

Although the majority of children with seizures have idiopathic epilepsies yet, a significant minority have identifiable etiologies ***(Berg et al., 2010).***

This can be summarized in the following table.

Table (2): Cause 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 nevus
Infections	Incontinentia pigmenti
Encephalitis*	**System disorders**
Meningitis*	Vasculitis (CNS or systemic)
Brain abscess	Systemic lupus erythematosis
Metabolic conditions	Hypertensive encephalopathy
Hypoglycemia*	Renal failure
Hypocalcaemia	Hepatic encephalopathy
Hyponatremia	Cerebral venous thrombosis
Hypomagnesemia	
Hypernatremia	**Others**
Storage diseases	Trauma*
Reye syndrome	Tumour
Degenerative disorders	Febrile*
Porphyria	Idiopathic*
Pyridoxine dependency and deficiency	Familial
Poisoning	
Lead	
Cocaine	
Drugs toxicity	
Drug withdrawal	
**Common*	

(Berg et al., 2010)

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)***.

In a large study to classify seizurs and epilepsy syndromes, 58% were localization related, 29% generalized and 12% undetermined ***(Luders al et., 2003).***

Table (3): International classification of epileptic seizures:

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)

Etiological classification of epilepsy:

Epilepsy is divided into four main categories:

Idiopathic epilepsy—defined as epilepsy of predominately genetic or presumed genetic origin and in which there is no gross neuroanatomic or neuropathologic abnormality. Included here are epilepsies of presumed multigenic or complex inheritance, but for which currently the genetic basis has not been elucidated ***(Ferrie, 2010).***

Symptomatic epilepsy—defined as epilepsy of an acquired or genetic cause, associated with gross anatomic or pathologic abnormalities, and/or clinical features, indicative of underlying disease or condition. We thus include in this category developmental and congenital disorders where these are associated with cerebral pathologic changes, whether genetic or acquired (or indeed cryptogenic) in origin. Also included are single gene and other genetic disorders in which epilepsy is only one feature of a broader phenotype with other cerebral or systemic effects ***(Guerrini, 2010).***

Provoked epilepsy—defined here as an epilepsy in which a specific systemic or environmental factor is the predominant cause of the seizures and in which there are no gross causative neuroanatomic or neuropathologic changes. Some ‘‘provoked epilepsies’’ will have a genetic basis and some an acquired basis, but in many no inherent cause can be identified. The reflex epilepsies are included in this category (which are usually genetic) as well as the epilepsies with a marked seizure precipitant ***(Wolf, 2010).***

Cryptogenic epilepsy—defined here as an epilepsy of presumed symptomatic nature in which the cause has not been identified. The number of such cases is diminishing, but currently this is still an important category, accounting for at least 40% of adult-onset cases of epilepsy ***(Shorvon et al., 2011).***

Table (4): Suggested scheme for an etiological classification of epilepsy:

Main category	Subcategory	Examples
diopathic 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; pyridoxinedependent 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
	Cerebral infection	Viral meningitis and encephalitis; bacterial meningitis and abscess; malaria; neurocysticercosis, tuberculosis; HIV
	Cerebrovascular disorders	Cerebral hemorrhage; cerebral infarction; degenerative vascular disease; arteriovenous malformation; cavernous hemangioma
	Cerebral immunologic disorders	Rasmussen encephalitis; SLE and collagen vascular disorders; inflammatory and immunologic disorders
	Degenerative and other neurologic Conditions	Alzheimer disease and other dementing disorders; multiple sclerosis and demyelinating disorders; hydrocephalus and porencephaly
Provoked epilepsy	Provoking factors	Fever; menstrual cycle and catamenial epilepsy; sleep-wake cycle; metabolic and endocrine-induced seizures; drug-induced seizures; alcohol and toxin-induced seizures
	Reflex epilepsies	Photosensitive epilepsies; startle-induced epilepsies; reading epilepsy; auditory-induced epilepsy; eating epilepsy; hot-water epilepsy
Cryptogenic epilepsies	the causes of the cryptogenic epilepsies are ‘‘unknown.’’ However, these are an important category, accounting for at least 40% of epilepsies encountered in adult practice and a lesser proportion in pediatric practice.	

(Shorvon et al., 2011)

In their recent report, the ILAE Commission for Classification of the Epilepsies has addressed etiology and divided epilepsiesinto three categories (genetic, structural/ metabolic, unknown cause), but they do not list etiologic categories any further ***(Berg et al., 2010)***.

Status epilepticus:

Status epilepticus is a potentially life-threatening condition in which a person either has an abnormally prolonged seizure or does not fully regain consciousness between recurring seizures. Although there is no strict definition for the time at which a seizure turns into status epilepticus, most people agree that any seizure lasting longer than 5 minutes should, for practical purposes, be treated as though it was status epilepticus. There is some evidence that 5 minutes is sufficient to damage neurons and that seizures are unlikely to end on their own by that time ***(NINDS, 2013).***

Status epilepticus affects about 195,000 people each year in the United States and results in about 42,000 deaths. While people with epilepsy are at an increased risk for status epilepticus, about 75 percent of people who develop this condition have no previous seizure history. These cases often result from tumors, trauma, or other problems that affect the brain and may be life-threatening ***(Koepp et al., 2005).***

While most seizures do not require emergency medical treatment, someone with a prolonged seizure lasting more than 5 minutes may be in status epilepticus and should be taken to an emergency room immediately. It is important to treat a person with status epilepticus as soon as possible ***(Thomas, 2007).***

The mortality rate of status epilepticus can be fairly high (about 20 percent), especially if treatment is not initiated quickly. One study showed that 80 percent of people in status epilepticus who received medication within 30 minutes of seizure onset eventually stopped having seizures, whereas only 40 percent recovered if 2 hours had passed before they received medication ***(NINDS, 2013).***

Doctors in a hospital setting can treat status epilepticus with several different drugs and can undertake emergency life-saving measures, such as administering oxygen, if necessary. With optimal neurological care, adherence to a medication regimen, and a good prognosis (no known underlying uncontrolled brain or other organic disease) an individual in good health—even someone who has been diagnosed with epilepsy—can survive with minimal or no brain damage, and can decrease their risk of death, and even avoid these seizures in the future ***(Drislane et al., 2009).***

Status epilepticus can be divided into two categories: convulsive (in which outward signs of a seizure are observed) and nonconvulsive (which has o outward signs and is diagnosed

by an abnormal EEG). Nonconvulsive status epilepticus may appear as a sustained episode of confusion or agitation in someone who does not ordinarily have that kind of mental impairment. While this type of episode may not seem as severe as convulsive status epilepticus, it should still be treated as an emergency ***(Kaplan, 2006).***

About half of the patients with seizures would become seizure free with the first antiepileptic drugs (AED), assuming the choice of medication and the drug dose were correct in patients who continue to have seizures on the first AED, further monotherapy and even polytherapy attempts would make another 15% seizure free hence leaving about one third of the patients refractory (drug resistant) ***(Kwan et al., 2011).***

Intractable epilepsy:

Definition

Traditionally, therapeutic failure of three antiepileptic drugs (AEDs) defined intractability ***(Brodie and Kwan, 2002).***

With many new AEDs available in recent years, it might have been expected that more, rather than fewer, drug trials would be recommended before determining intractability. However, several prospective case series have shown that a high likelihood of medical intractability can be identified after two unsuccessful trials, as with each AED failure, the likelihood of successful treatment with other drugs diminishes ***(Brodie and Barry, 2013).***