Developmental Assessment of Infants and Children with Drug Resistant Epilepsy on Ketogenic Diet

Thesis

Submitted for Partial Fulfillment of
Master Degree in **Pediatrics**

By

Ereny Alkess Dawood Habib
M.B.B.Ch., Faculty of Medicine 2011
Faculty of Medicine- Ain Shams University

Under Supervision of

Prof. Dr. Neveen Tawakol Younis
Professor of Pediatrics
Faculty of Medicine-Ain Shams University

Dr. Shaymaa Maher Deifalla
Assistant Professor of Pediatrics
Faculty of Medicine-Ain Shams University

Faculty of Medicine
Ain Shams University
2020

Acknowledgments

First and foremost, I feel always indebted to ***GOD*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Dr. Neveen Tawakol Younis****, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Dr. Shaymaa Maher Deifalla****, Assistant Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her sincere efforts, fruitful encouragement.*

*I would like to express my hearty thanks to all my family and my colleague (****Christina Adel****) for their support till this work was completed.*

Ereny Alkess Dawood Habib

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List of Abbreviations

AEDs	**:**	Antiepileptic drugs
ADEAF	**:**	Autosomal dominant epilepsy with auditory features
ADNFLE	**:**	Autosomal-dominant nocturnal frontal lobe epilepsy
BECTS	**:**	Benign epilepsy with centrotemporal spikes
BFNE	**:**	Benign familial neonatal epilepsy
CSF	**:**	Cerebrospinal fluid
CSSS	**:**	Chalfont seizure severity scale
CAE	**:**	Childhood absence epilepsy
CT	**:**	Computed tomography
CAU	**:**	Control as usual
EME	**:**	Early myoclonic encephalopathy
EEG	**:**	Electroencephalography
CSWS	**:**	Epileptic encephalopathy with continuous spike-and-wave during sleep
FSE	**:**	Fast spin-echo
FLAIR	**:**	Fluid attenuation inversion recovery
FSIQ	**:**	Full Scale Intelligence Quotient
GABA	**:**	gamma-amino butyric acid
IQR	**:**	inter-quartile range
JAE	**:**	Juvenile absence epilepsy
JME	**:**	Juvenile myoclonic epilepsy

KD	**:**	Ketogenic diet
LKS	**:**	Landau-Kleffner syndrome
LCAD	**:**	Long chain acyl dehydrogenase deficiency
MRI	**:**	Magnetic resonance imaging
mTOR	**:**	Mammalian target of rapamycin
MCAD	**:**	Medium chain acyl dehydrogenase deficiency
MEI	**:**	Myoclonic epilepsy in infancy
PME	**:**	Progressive myoclonus epilepsies
MCAD	**:**	Short chain acyl dehydrogenase deficiency
SB5	**:**	Stanford–Binet Fifth Edition
SPSS	**:**	Statistical Package for Social Science
WHO	**:**	World Health Organization

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INTRODUCTION

Epilepsy is a neurological disorder that is treated with antiepileptic drugs (AEDs) in the majority of the patients. However, AED are sometimes not efficacious. About one-third of patients suffer from intractable epilepsy ***(IJff et al., 2016)***.

Intractable/drug resistant epilepsy refers to seizures that remain uncontrolled despite treatment with two or more first-line antiepileptic drugs (AEDs), administered serially as mono therapies or in combination, with the dose reaching the maximum tolerated dose for an appropriate treatment course ***(Zhu et al., 2016).***

Furthermore, patients often experience side effects that lead to discontinuation of the drug. For these patients, alternative non-pharmacological treatment options are available, including the ketogenic diet (KD) ***(IJff et al., 2015).***

Ketogenic diet (KD) is a non-pharmacologic treatment for children with drug resistant epilepsy. The efficacy of the KD has been established by several multicentre studies and one randomized controlled trial. The randomized trial that further established the efficacy of KD was conducted in children and adolescents aged 2-16 years ***(van der Louw et al., 2016).***

Ketogenic diet is a high-fat, adequate-protein, and low carbohydrate diet administered under medical supervision,

which tends to maintain chronic ketosis in the body as well as provide adequate protein and calories for growth and development ***(Sharma et al., 2013).***

Notably, some authors believe that KD is more effective than most of the newer anticonvulsive medications ***(Ashrafi et al., 2017).***

KD is used in various forms including classic KD, medium-chain triglyceride (MCT) diet, long-chain triglyceride (LCT) diet, modified Atkins diet and low glycemic index diet. It has shown to decrease seizure frequency by about 40%–50% from baseline in selected groups of patients and has a prolonged beneficial effect even after its discontinuation. The International Ketogenic Diet Study Group recommends that KD should be considered strongly in a child who fails two to three anticonvulsant medications, regardless of age or gender ***(Agarwal et al., 2017)***.

The KD is also an important co adjuvant treatment for most refractory and generalized epilepsies, such as Dravet, Doose, Lennox-Gastau and West syndromes ***(Wang and Lin, 2013).***

Clinical and epidemiologic studies indicate that chronic epilepsy is followed by long-term behavioural changes and cognitive degeneration even in an optimal state of antiepileptic drug therapy ***(Lima et al., 2014)***.

Cognitive comorbidities, including intellectual disability of variable severity, specific learning disorders are common in children with epilepsy, and can have an even greater impact on quality of life than do seizures. The underlying cause(s) of these comorbidities is not clear. Although they are more likely to be observed in individuals with early-onset, pharmaco resistant epilepsy with frequent seizures, such as epileptic encephalopathy, transient cognitive impairment can also occur as a result of brief epileptiform discharges.***(Ghacibeh & Fields, 2015)***.

Other causes that might contribute to the cognitive compromise include antiepileptic drugs for example phenobarbital and valproic acid are associated with greater concern of cognitive impairment (***Nickels et al., 2016)***.

Cognitive and behavioral comorbidities are often under diagnosed and consequently, undertreated. In a population-based study of school children with epilepsy, 80% with active epilepsy had either a behavioral disorder and/or cognitive impairment (IQ ≤85), with up to 40% having a Full Scale Intelligence Quotient (FSIQ) <70 (***Reilly et al., 2014)***.

A broad scope of cognitive deficits and behavioral abnormalities is associated with intractable epilepsy. However, few studies have investigated the effects of add-on therapy with KD on the neurobehavioral development.***(Zhu et al., 2016)***.

Ijff et al. in ***2016*** studied 50 patient with drug resistant epilepsy, 28 patient on KD (intervention group) and 22 a care as usual group (control) aged between 1 and 18 years, they followed them up for 4 months, the study showed a positive impact of the KD on behavioral and cognitive functioning in children and adolescents with refractory epilepsy ***(Ijff et al., 2016).***

Zhu et al., 2016 studied 42 drug resistant epileptic children, Who were starting treatment with the classic KD protocol. The total development quotient was assessed before and after 3, 6, 12 and 18 months of KD treatment. They aged >6 months and < 6 years. They found that KD treatment tend to be associated with improved neurobehavioral development (***Zhu et al., 2016).***

AIM OF THE STUDY

1- Assess the impact of KD on developmental progress of children with drug resistant epilepsy

2- Assess its efficacy regarding seizure frequency and severity.

Chapter 1

EPILEPSY

Conceptual definition of seizure and epilepsy – 2005 report

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure ***(Fisher et al., 2014).***

Epilepsy: Epilepsy has traditionally been referred to as a disorder or a family of disorders, rather than a disease, to emphasize that it is comprised of many different diseases and conditions. The term disorder implies a functional disturbance, not necessarily lasting; whereas, the term disease may (but not always) convey a more lasting derangement of normal function. Many heterogeneous health problems, for example, cancer or diabetes, comprise numerous subdisorders and are still considered to be diseases. The term "disorder" is poorly understood by the public and minimizes the serious nature of epilepsy. The ILAE and the International Bureau for Epilepsy (IBE) have recently agreed that epilepsy is best considered to be a disease.

Operational (practical) clinical definition of epilepsy:

Epilepsy is a disease of the brain defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring >24 h apart

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years ***(Fisher et al., 2014).***

Drug resistant Epilepsy:

Intractable/drug resistant epilepsy refers to seizures that remain uncontrolled despite treatment with two or more first-line antiepileptic drugs (AEDs), administered serially as mono therapies or in combination, with the dose reaching the maximum tolerated dose for an appropriate treatment course ***(Zhu et al., 2016).***