Plasma Free Carnitine In Children with Epilepsy

Thesis
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By

Sawsan Fetouh Anwar Ghanem

M.B.B.Ch

Faculty of medicine, TantaUniversity

Under supervision of

Prof. Dr. Nancy Abd El-Aziz Soliman

Professor of Pediatrics

Faculty of medicine, Ain Shams University

Prof. Dr. Manal Mohamed Abd El- Aziz

Professor of Clinical Pathology

Faculty of medicine, Ain Shams University

Dr. Iman Ali Abd El-Hamid

Assistant Professor of Pediatrics

Faculty of medicine, Ain Shams University

Ain Shams University

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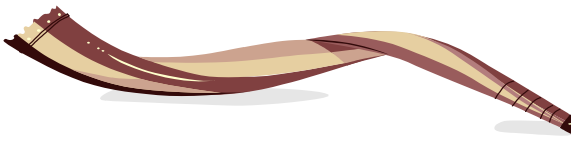

Sawsan Ghanem

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LIST OF ABBREVATIONS

AEDs	Antiepileptic drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BFNS	Benign familial neonatal seizures
BMEI	Benign myoclonic epilepsy of infancy
CAE	Childhood absence epilepsy
CK	Creatine phosphokinase
CNS	Central nervous system
COA	Coenzyme A
CPR	Cardiopulmonary resuscitation
CPS	Complex partial seizures
CPT	Carnitine palmitoyltransferase
CSF	Cerebrospinal fluid
CT	Computed tomograph
ECG	Echocardiogram
EEG	Electroencephalogram
ETCSA	Epilepsy with generalized tonic-clonic seizures on awakening
FC	Free carnitine
GABA	Gama amino butyric acid
GGT	Gamma-glutamyl transpeptidase
GSW	Generalized spike wave
GTC	Generalized tonic-clonic
IGE	Idiopathic generalized epilepsy
ILAE	The international league against epilepsy
IV	Intravenous

JAE	Juvenile absence epilepsy
JME	Juvenile myoclonic epilepsy
LCHAD	Long-chain acyl-COA dehydrogenase
MCAD	Medium chain acyl-COA dehydrogenase
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
OCTN2	Organic cation\carnitine transport
P	Probability
PCOS	Polycystic ovary syndrome
PFC	Plasma free carnitine
rCBF	regional cerebral blood flow
rCGM	regular cerebral glucose metabolism
SD	Standered deviation
SE	Status epilepticus
SIDS	Sudden infant death syndrome
SPS	Simple parial seizures
SUDEP	Sudden unexpected death in epilepsy
TPN	Total parental nutrition
VPA	Valproic acid

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INTRODUCTION

An epileptic seizure is a transient occurrence of signs and or symptoms due to abnormal excessive or synchronous neuronal activity in the brain ***(Fisher et al., 2005).***

Epilepsy is usually controlled by the administration of antiepileptic drugs. The type of seizure and the specific epileptic syndrome play a role in the selection of anticonvulsants, probably because of the different Pathophysiologic mechanisms ***(Kaindl et al., 2006)***.

Valproate is extensively metabolized by the liver via glucuronic acid cojugation, mitochondrial B- and cytosolic omega-oxidation to produced multiple metabolites (4-ene-valproate and 2, 4-diene-valproate), some of which may be involved in its hepatotoxicity ***(Lheureux and hantson, 2009)***.

Some hypotheses have implicated direct hepatic damage by valproate metabolites , impaired hepatic metabolism of ammonia ***(Panda and Radhakrishnan, 2004)*** and increase ammonia production by the kidneys as causes of hyperammonemia induced by valproate ***(Warter et al., 1993***).

Hyperammonemia has also been suggested to be a marker for other metabolic abnormalities as free fatty acids. It is considered as an indication for carnitine deficiency encountered in the same group of patients ***(Opala et al., 1991)***. In addition, carnitine deficiency has been linked to hepatic complication associated with valproate use ***(Murakami et al., 1990)***.

Carnitine is an amino acid derivative present in most human tissue particularly liver and muscles. It is mainly supplied from dietary amino acid, particularly meat and dairy products ***(Blass, 1989).***

However, it can be produced by endogenous synthesis in the liver and kidney from dietary methionine and lysine and by renal reabsorption. Carnitine is an essential cofactor required for the transport long-chain fatty acids across mitochondrial membrane for B-oxidation, which result in energy production needed for metabolism **(*Vaz and Wanders, 2002)***.

Carnitine is also involved in oxidation of ketone bodies, glucose and various amino acids ***(Borum and Bennett, 1986)***. It mops up certain acryl coenzyme A (Acyle-CoA) groups and toxic intermediates that impair the citric acid cycle, urea cycle, pathways for gluconeogenesis and fatty acid oxidation from the mitochondria and peroxisomes during acute clinical crisis ***(Vaz and Wanders, 2002)***.

Carnitine deficiency occurs in primary inborn errors of metabolism as mitochondrial disorders, fatty acid oxidation disorders and glutaric aciduria, nutritional Problems, defective renal reabsorption and by intake of some Medication as valproate ***(Bohan et al., 2001)***.

The most important consequence of carnitine deficiency is impaired energy metabolism. Manifestation of carnitine deficiency include muscle weakness, hypotonia, Nausea and vomiting, fatigue, recurrent infection, failure to thrive, poor appetite and poor concentration, apathy and headache ***(Shapira and Gutman, 1991)***.

AIM OF THE WORK

The aim of the present study was to evaluate level of plasma free carnitine in epileptic children treated with antiepileptic drugs monotherapy or polytherapy and newly diagnosed patients before start of their therapy.

EPILEPSY

Definition of epilepsy:

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).***

Epilepsy is a frequent neurological disease in childhood characterized by recurrent Seizures and sometimes with major effect on social, behavioural and cognitive development ***(Lieven Lagae, 2008).***

Seizures are single or paroxysmal events arising from a bnormal excessive hypersynchrous discharges from central nervous system neurons, and range in severity from symptoms not readily apparent to an observer to dramatic convulsion ***(Lowensstein and Cloyd, 2008).***

During a seizure, the epileptic activity in the brain can be seen as a series of ″spikes "or ″spikes and waves" in EEG recording. These ″spikes"or ″spikes and waves″ are called the ″electrographic″ seizure. The behavior of patient during the epileptic attack is called the (clinical) seizure. If the clinical seizure involves muscle spasm it is called a ″convulsion″ ***(Burnham, 2002).***

Epidemiology and morbidity indices:

- **Age incidence:**

Epilepsy is the second most common chronic neurological disorder after stroke approximately 0.5-2% of population ***(Boon et al., 2001).*** It is estimated that 0.5-1% of all children have epilepsy, with the majority presenting during infancy or early childhood ***(Ottman, 2001).***

(Johnston, 2011) reported that the cumulative life time incidence of epilepsy is 3% and more than half of cases begin in childhood.The overall incidence of childhood epilepsy from birth to 10 years is

approximately 5-7 cases per 10,000 children per year as reported by ***(Cowan, 2002).***

The incidence in the first year of life is about 120 in 100.000. Between one and ten years of age, the incidence is about 40-50 in 100,000 and then drops in the older ages to about 1% ***(Hauser and Hesdorfen, 1990).***

- **Sex :**

Some studies found that males were more affected than females, and suggested that females might find it easier to conceal their fits ***(Freitag et al., 2001).***

- **Incidence by seizure type:**

Generalized tonic–clonic or various types of partial seizures dominate about 75% of childhood epilepsy syndromes and partial seizures seemed to occur more often than generalized seizures ***(Kotosopoules et al., 2002)***. Absence epilepsies account for approximately 15% and other generalized epilepsies account for only 10% ***(Camfield et al., 1996).***

- **Prevalance of epilepsy:**

Eilepsy is one of the most prevalent non communicable neurologic condition and an important cause of disability and mortality**.** Since mortality is high early in the course of epilepsy and spontaneous remission may occur ***(Sander, 2004)***.

The prevalence in developing countries is about 4 to 5 times the prevalence in developed countries and this may be related to the poor antenatal care, prematurity, birth injuries, malnutrition and multiple infections ***(Okasha, 1988)***.

In Egypt, ***(Mekky, 1981)*** studying the epidemiology of epilepsy demonstrated prevalence 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 while ***(EL-Khyat et al., 1994)*** studying the prevalence of epilepsy in children, reported a prevalence of 3.5 per 1000 population. And ***(Massoud, 1997)*** in this study on 195 school children in cairo, reported a lower overall prevalence of 1.9 per 1000.

Mechanisms and pathophysiology of seizures:

Although the precise mechanisms of seizures are unknown, several physiologic factors are responsible for the development of a seizure. To initiate a seizure, there must be a group of neurons that are capable of generating a significant discharge and impairment of the γ-aminobutyric acid (GABA) inhibitory system. Evidence suggests that transmission of seizure discharge depends on excitatory amino acid neurotransmitters (glutamate, aspartate) that may have a role in producing neuronal excitation by acting on specific cell receptors. Seizures may arise from lesions in the temporal lobe or areas of neuronal death and when the abnormal tissue is removed surgically, the seizures are likely to cease ***(Johnston, 2011)***.

Two hypotheses have been suggested to explain the origin of seizures after brain injury. One suggests that inhibitory neurons are selectively damaged and the remaining excitatory neurons become hyperexcitable. The other hypothesis suggests that aberrant excitatory circuits are formed as part of reorganization after injury ***(Johnston, 2011)***.

Seizures are more common in infants and certain seizures in pediatrics are age specific as infantile spasms; this observation suggests that the underdeveloped brain is more susceptible to specific seizures than in the brain of an older child or adult. This is consistent with basic science data indicating that the immature brain is more excitable than the mature brain,

reflecting the greater influence of excitatory glutamate-containing circuits ***(Johnston, 2011)***.

Furthermore, functional immaturity of the substantia nigra has an integral role in the increased seizure susceptibility of the immature brain and development of generalized seizures. Additionally, it is suggested that substantia nigra outflow tracts modulate and regulate seizure dissemination but are not responsible for the onset of seizures ***(Johnston, 2011)***.

Causes of epilepsy:

Epilepsy can be defined in terms of etiology (cause). There are three types of epilepsy: idiopathic, symptomatic, and cryptogenic. About 30% of childhood epilepsy is idiopathic in which there is no apparent underlying cause and the brain appears to be completely normal. In patients with idiopathic epilepsy, the seizures are thought to be caused by genetic factors (having no identifiable physical cause) ***(Burnham, 2002).***

In some types of epilepsy the genetic factor is strong and inheritance follows simple Mendelian rules. In most cases of epilepsy, however, inheritance is "multifactorial" meaning that several genes are involved. In these cases, inheritance does not follow simple Mendelian rules ***(Burnham, 2002)***. Between 25% and 45% of childhood epilepsy is symptomatic which is caused by known structural abnormalities or damage in the brain or by an underling disease (having an identifiable physical cause) such as: congenital brain malformation, injury or trauma (at birth or later), brain hypoxia, infection with permanent damage, tumor, stroke, tangle of blood vessels, or metabolic disorder ***(Chapman, 1998).***

Cryptogenic epilepsy (from the Greek word "kryptos" meaning "hidden") in which the child's epilepsy is symptomatic, but cannot locate the underlying cause and the child usually has developmental delay or abnormal finding on neurological examination. Sometimes doctors call this

type of epilepsy "probably symptomatic". The terms “idiopathic epilepsy” and “cryptogenic epilepsy” are sometimes used interchangeably, especially in older books and articles. By definition, the cause of cryptogenic epilepsy is unknown ***(Donner et al, 2006).***

It is often assumed to be caused by a brain lesion that is not visible on CT scan or MRI. Because the quality of these tests has improved over the last several decades, the proportion of cases that are defined as cryptogenic has decreased. In other cases, a child whose epilepsy is considered cryptogenic at first is later diagnosed with a metabolic or mitochondrial disease, and the classification changes to symptomatic epilepsy ***(Donner et al, 2006).***

- **Classification of seizure type**

The type of seizure depends upon several factors. One of the most important factors is where in the brain the abnormal electrical discharge occurs. The four lobes of the brain (frontal, temporal, parietal and occipital) where key regions of the brain are located. Strength and sensation are laid out along the border of the frontal and parietal lobes, with strength more toward the front (frontal) and skin sensation more toward the back (parietal) of the strip ***(fisher, 2005).***

Moving laterally and down the brain are control areas for trunk, arm, hand, fingers, face, lips, and tongue, with tongue most laterally and inferiorly on the motor strip ***(fisher et al., 2005)***.

A talking center, called Broca´s area, is located in the left frontal lobe in front of the motor strip, and a speech comprehension area called Wernicke's area in the left temporal- parietal region for most right handers. Speech centers may be on the right or both sides for left-handers. Visual perception is governed from the posterior poles of the occipital lobes. In general, brain functions are crossed: the left side of the brain receives