Protein Aversion in Children with Epilepsy on Valproate Therapy

Thesis

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List of Abbreviations

Abb.	Full term
5-HT	*5hydroxy tryptamine*
ABAT	*4-aminobutyrate aminotransferase*
ACTH	*Adrenocorticoyropin*
AED	*Antiepileptic drugs*
ALDH5A1	*Aldehyde dehydrogenase 5 family, member A1*
ALT	*Alanine aminotransferase*
AMPA	*Amino-3hydroxy-5-methyl-isoxasole propionic acid*
Ca	*Calcium*
CBC	*Complete blood count*
Cl	*Chloride*
CNS	*Central nervous system*
CNS	*Central nervous system*
CP	*Cerebral Palsy*
CPS	*Carbamoyl phosphate synthetase*
CPS	*Carbamoyl phosphate synthetase*
CSF	*Cerebro-spinal fluid*
CT	*Computed tomography*
DSM	*Diagnostic and Statistical Manual Disorders*
EDTA	*Ethylene diaminetetra acetic acid*
EEG	*Electo encephalography*
GABA	*Gamma-amino-butyric acid*
GAD	*Glutamic acid decarboxylase*
GTC	*Generalized tonic clonic*
GTC	*Generalized tonic clonic*
HDAC	*Histone deactylase*

List of Abbreviations cont...

Abb.	Full term
HDAC	*Histone deactylase*
HS	*Highly significant*
IBM SPSS	*Statistical package fo social science*
IGE	*Idiopathic generalized epilepsy*
ILAE	*International league of epilepsy*
IQ	*Intelligence quotient*
IQR	*Interquartile range*
K	*Potassium*
L-carnitine	*Levocarnitine*
LPI	*Lysinuric protein intolerance*
MEG	*Magnetoencephalography*
MRI	*Magnetic resonance imaging*
NA	*Not applicable*
Na	*Sodium*
NADH	*Nicotinamide adenine dinucleotide*
NADPH	*Nicotinamide adenine dinucleotide phosphate*
No	*Number*
NS	*Non significant*
OCTN	*Organic zwitterions/cation transporters*
OGDH	*Oxoglutrate dehydrogenase*
PCO	*Polycystic ovarian syndrome*
PET	*Position-emission-tomogram*
S	*Significant*
SD	*Standard deviation*
Sig	*Significance*
SPECT	*Single- photon emission-tomogram*

List of Abbreviations cont...

Abb.	Full term
UCD	*Urea cycle disorder*
VHE	*Valproate induced hyperammonemic encephalopathy*
VNS	*Vagal nerve stimulation*
VPA	*Valproic acid*

Abstract

Introduction: Valproic acid is widely used drug for treatment of epilepsy in children. Although there weren't much data about the occurance of protein aversion in patients on valproate therapy, yet, observing many patients on valproate whose parents complaining of protein aversion provoked us to conduct this study. Protein aversion has been found to be a common feature of urea cycle disorders. As it is well known that Valproic acid may cause hyperammonemia through carnitine deficiency created by its inhibition of mitochondrial enzymes in the urea cycle. *so, we assumed that protein aversion may be related to increased ammonia level caused by valproate.*

Aim: The aim of the present study is to study the relation between protein aversion and valproate therapy in children with epilepsy and whether it is related to ammonia level or not.

Methodology: Our cross sectional study was conducted on two groups (patient group and control group). Each group included 45 children from 2 to 16 years old fulfilling the inclusion criteria recruited from Pediatric Neurology Clinic and Outpatients' Clinic, Children's Hospital, Faculty of Medicine, Ain Shams University during the period of September 2016 to December 2017. Both groups were subjected to detailed dietary history including questionnaire for food frequency consumption. Data were compared between the two study groups and in the patient group, data were compared between before and after valproate therapy. Also both groups were subjected to ammonia level assay.

Results: Protein aversion was seen in more than half (55.6%) of children on valproate. This was seen especially for red meat (46.7%). Majority of the patients developed aversion after starting valproate therapy (84%) by 7.84 ± 3.28 months. However, ammonia level had no significant correlation to protein aversion. Also, l-carnitine intake didn't show effect on protein aversion.

Conclusion: Protein aversion was related to valproate therapy in children with epilepsy.

Recommendation: Regular nutritional assessment for children on valproate therapy is advisable. Also, further studies with larger scale on patients with idiopathic epilepsy exclusively on valproate therapy are recommended.

INTRODUCTION

Valproate (**VPA**), is a medication primarily used to treat epilepsy especially absence seizures, generalized tonic clonic. It can be given oral or parentral. Common side effects include nausea, vomiting. Serious side effects can include liver problems and regular monitoring of liver function tests is therefore recommended. It is known to cause serious abnormalities in the baby if taken during pregnancy ***(Roger et al., 2007).***

Valproic acid is one of common drugs for treatment of epilepsy in children. It was an observation in our clinic that many children who are on valproic acid treatment showed aversion for protein diet. Looking into published data, There was no studies regarding relationship between valproic acid and protein aversion so, our study aims to clarify if there is a relationship between valproic acid and protein aversion or not and to assess this relation, if present.

It is well known that Valproic acid may cause hyperammonemia through carnitine deficiency created by its inhibition of mitochondrial enzymes in the urea cycle ***(Carol et al., 2007).***

Protein aversion is a common feature of urea cycle disorders (UCD) and may serve as a diagnostic clue in patients presenting with food refusal, recurrent vomiting, behavioral

problems, mental retardation, and "unexplained" episodes of altered consciousness ***(Gardeitchik et al., 2012)***.

Patients with Lysinuric protein intolerance (LPI) have hyperammonemia after ingestion of normal amounts of dietary protein. As a protective mechanism, most patients develop strong aversion to protein-rich foods early in life ***(Tanner et al., 2007)***.

AIM OF THE WORK

The aim of the present study is to study the relation between protein aversion and valproate therapy in children with epilepsy and whether it is related to ammonia level or not.

Chapter One

EPILEPSY

Epilepsy is one of the most common chronic neurologic - conditions, affecting as many as 45 million people worldwide. The prevalence of epilepsy in the United States has been estimated at 6 to 8 per 1000 population, with an incidence of 26 to 40 per 100,000 person-years ***(Asconapé, 2010)***.

The incidence of epilepsy has a bimodal distribution, with the highest risk observed in infancy and old age. About two-thirds of the epilepsies are localization-related or partial, and a third generalized. Of the localization-related epilepsies, about two-thirds remain of unknown etiology despite an adequate workup. Approximately 60% to 70% of patients with epilepsy have an adequate response to antiepileptic drug therapy ***(Asconapé, 2010).***

According to international league of epilepsy (***ILAE***), a person is considered to have epilepsy if they meet any of the following conditions at least two unprovoked (or reflex) seizures occurring greater than 24 hours apart, 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 or diagnosis of an epilepsy syndrome ***(Fisher et al., 2014)***.

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 disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. Translation: a seizure is an event and epilepsy is the disease involving recurrent unprovoked seizures. As described by ILAE in 2005 ***(Fisher et al., 2005).***

Mechanisms:

The pathophysiology of epilepsy involves alterations of normal physiological processes. An epileptic seizure is produced by synchronous and sustained firing of a population of neurons in the brain. The behavioral manifestations of a seizure reflect the function of the cortical neurons involved in the generation and spread of abnormal electrical activity. Epileptogenicity refers to the excitability and synchronization of neuronal networks that produce epileptiform activity in the brain. Both excitatory and inhibitory influences may be altered, creating a predisposition to excessive synchrony within neuronal populations ***(Foldvary-Schaefer and Wyllie, 2007).***

Multiple factors contribute to epileptogenesis such as intracellular, intrinsic membrane, and extracellular mechanisms. Three key elements contribute to the development of the hyperexcitability needed for epileptogenesis: 1) the capability of