Effect of antiepileptic drugs on thyroid profile in Epileptic children and adolescents

Case control study

Thesis
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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
ورَسُولُهُ والْمُؤْمِنُونَ

صدق الله العظيم

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Fairouz Ahmed Abdel-MoneimTawfik

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List of Abbreviations

AED(s)	Antiepileptic drug (s)
apoA-I	Apolipoprotein A- I
apoB	Apolipoprotein B
BHS	Breath-holding spells
CBZ	Carbamazepine
CT	Computed tomography
DHEAS	Dehydroepiandrosterone sulfate
ECG	Electrocardiogram
EEG	Electroencephalogram
FT3	Free triiodothyronine
FT4	Free thyroxine
GABA	g-aminobutyric acid
HDL-C	High-density lipoprotein cholesterol
HPT	Hypothalamic pituitary thyroid
HRQOL	Health-related quality of life
ILAE	International League Against Epilepsy
IQ	Intelligence quotient
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
mIU/L	Milliunits per litre
MRI	Magnetic resonance imaging
NEAD	Non-epileptic attack disorder
ng/ml	Nanogram per milliliter
OXC	Oxycarbazepine
PB	Phenobarbital
pg/ml	Picogram per milliliter

PVN	Para-ventricular nucleus
SUDEP	Sudden unexpected death in people with epilepsy
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroid binding globulin
TC	Total cholesterol
TG	Triglycerides
TRH	Thyrotropin releasing hormone
TRs	Thyroid hormone receptors
TSH	Thyroid stimulating hormone
TSHR	Thyrotropin receptor
VPA	Valproic acid

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Introduction

Epilepsy is one of the serious neurological disorders which results in profound morbidity and mortality **(El-Tallawy et al., 2013)**.

The annual incidence ranges from 5-7 per 10 000 in the age group of 0-15 years, and being the most common neurological disorder of childhood **(Nettekoven et al., 2008).**

Diagnostic criteria and treatment alternatives for childhood epilepsies may differ in terms of disease course and outcome. Although many alternatives have been recommended for treatment including vagus nerve stimulation, epilepsy surgery and ketogenic diet, the primary treatment of choice is the use of antiepileptic drugs (AEDs) **(Toledano and Gil-Nagel, 2008).**

Epilepsy treatment should be goal oriented and approached in an objective fashion. Seizure elimination or significant seizure reduction, reducing seizure severity, and maintaining normal lifestyle for patient and owner are all important considerations **(Podell, 2013).**

The treatment of childhood epilepsy is different from that of adult epilepsy because many epilepsy syndromes are specifically pediatric and maturational process requires prescribing these drugs according to age and weight **(Chiron, 2012).**

Knowledge of the essential properties, key indications and interactions of each antiepileptic drug will help to optimize efficacy and reduce adverse reactions **(Hadjiloizou and Bourgeois, 2007).**

Endocrine disorders are of major concern for clinicians who treat patients with epilepsy. This is even more important

during a stage of rapid growth, weight gain, skeletal and genital maturation as well as neurological development by the modulatory effects of hormones during childhood**.** Therefore, it is of importance for physicians and epileptologists to be well grounded in hormonal and/or metabolic alterations associated with epilepsy or AEDs possibly requiring regular monitoring of blood parameters, inducing further investigation and treatment or reevaluation and possibly alteration of AEDs treatment **(Luef and Rauchenzauner, 2009).**

Thyroid hormones have critical effects on protein synthesis and destruction, carbohydrate and lipid metabolism in all tissues. The presence of thyroid hormones is essential for the development of central nervous system. Thyroid hormone deficiency may cause growth and developmental disorders in children even if growth hormone levels are within normal limits **(Setian, 2007).**

AEDs lead to several degrees of impairment in thyroid hormone homeostasis by changing its biosynthesis, secretion, transport, metabolism and excretion **(Benedetti et al., 2005).**

Disturbances in thyroid hormone homeostasis associated with AEDs have been reported for the first time by **Oppenheimer and McPherson (1961).**

Since then, contradictory results have been reported, and the effects of AEDs on thyroid functions, particularly in children, have become a subject of debate for the clinicians **(Cansu et al., 2006; Hirfanoglu et al., 2007; Attilakos et al., 2009).**

Castro-Gago et al. (2007) stated that varying grades of subclinical hypothyroidism were observed in a number of children receiving long-term therapy with valproate (VPA) and Carbamazepine (CBZ) as AEDs**.**

However, **Verrotti et al. (2009)** noted that VPA monotherapy does not alter thyroid hormones. On the contrary, alterations of thyroid hormones occur in CBZ treated children however alterations are not associated with clinical or subclinical hypothyroidism.

Moreover, **Aggarwal et al. (2011)** concluded that CBZ and VPA therapy alters thyroid functions by decreasing FT4 levels. Compensation by increase in thyroid-stimulating hormone (TSH) is better with VPA.

Aim of the Work

To study the correlation between the administration of valproate and carbamazepine as monotherapy for controlling epileptic patients in childhood and adolescents and changes in the levels of thyroid hormones.

Chapter 1

Epilepsy in children and adolescents

Epilepsy is defined as a 'tendency to recurrent unprovoked seizures'. Epilepsy should be regarded as a symptom of an underlying condition although in some cases the underlying condition is a genetic epilepsy, also known as idiopathic epilepsy; in which seizures are the sole or predominant manifestation. A complete diagnosis of epilepsy should include the underlying cause, where this can be established **(Hart, 2012).**

An epileptic seizure is an episode of neurologic dysfunction in which abnormal neuronal firing is manifested clinically by changes in motor control, sensory perception, behavior, or autonomic function **(Pitkänen and Lukasiuk, 2009).**

Epilepsy is the condition of recurrent spontaneous seizures arising from aberrant electrical activity within the brain. While anyone can experience a seizure under the appropriate pathophysiological conditions, epilepsy suggests an enduring alteration of brain function that facilitates seizure recurrence. Epileptogenesis is the process by which the normal brain becomes prone to epilepsy **(Pitkänen and Lukasiuk, 2009).**

The complete process of epileptogenesis is not known for any single type of seizure. Broadly, reciprocal corticothalamic interaction is probably important in the generation of generalized seizures, whereas a local excitation–inhibition imbalance is the likely basis of partial seizures. Disorders of membrane ion channels are increasingly reported in epilepsy, but complex changes at receptor, membrane, cyto-architectural and system levels are probably involved in most cases. Modern pathological studies are beginning to define the