

*Prolactin, Thyroid hormones, and Growth
hormone levels in Epileptic children on
Antiepileptic drugs*

Thesis

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List of Abbreviations

• ACTH	Adrenocorticotrophic hormone
• ADH	Antidiuretic hormone
• AEDs	Anti-epileptic drugs
• ALT (SGPT)	Alanine transaminase
• AMPA	Alpha amino 3 hydroxy 5 methylisoxazole propionic acid
• AST (SGOT)	Aspartate transaminase
• AV block	Atrioventricular block
• BDZ	Benzodiazepines
• BECCT	Benign epilepsy of childhood with centrotemporal spikes
• BMEI	Benign myoclonic epilepsy of infancy
• BMI	Body mass index
• BOE	Benign occipital epilepsy
• BUN	Blood urea nitrogen
• CAE	Childhood absence epilepsy
• cAMP	Cyclic adenosine monophosphate
• CBZ	Carbamazepine
• CNS	Central nervous syndrome
• CT	Computerized tomography
• EEG	Electroencephalography
• ELISA	Enzyme linked immunosorbent assay
• FLAIR	Fluid attenuated recovery
• FSH	Follicle stimulating hormone
• GABA	Gamma amino butyric acid
• GAD	Glutaric acid decarboxylase
• Gamma GT	Gamma glutamyl transferase
• GBP	Gabapentin
• GH	Growth hormone
• GHBP	Growth hormone binding protein
• GHRH	Growth hormone releasing hormone
• GTC	Generalized tonic clonic convulsions
• hCG	Human chorionic gonadotropins
• HDL	High density lipoprotein
• HIV	Human immunodeficiency virus
• HLA	Human leukocyte antigen
• IGF-1	Insulin growth factor-1
• IGFBP3	Insulin growth factor binding protein 3
• ILAE	International league against epilepsy

• IM injection	Intramuscular injection
• IV injection	Intravenous injection
• JAE	Juvenile absence epilepsy
• JME	Juvenile myoclonic epilepsy
• LDH	Lactate dehydrogenase
• LGS	Lannox-Gastaut syndrome
• LH	Lutenizing hormone
• LTG	Lamotrogine
• MHD	10 monohydroxy metabolite
• MRI	Magnetic resonance imaging
• mRNA	Messenger ribonucleic acid
• MRS	Magnetic resonance imaging
• MSH	Melanocytes stimulating hormone
• NMDA	N-Methyl-D-aspartate
• OFC	Occipitofrontal circumference
• OXC	Oxcarbazepine
• PET	Positron emission tomography
• PET-FDG	Positron emission tomography-18 fluorodeoxyglucose
• PHB	Phenobarbital
• PHT	Phenytoin
• PRL	Prolactin
• PSW	Polyspike and Wave
• REM	Rapid eye movement
• RNA	Ribonucleic acid
• SPECT	Single photon emission computed tomography
• SPGR	Spoiled gradient recall images
• SW	Spike and Wave
• TBG	Thyroid binding globulin
• TCAs	Tricyclic antidepressants
• TLE	Temporal lobe epilepsy
• TRH	Thyrotropin releasing hormone
• TSH	Thyroid stimulating hormone
• VGB	Vigabatrin
• VPA	Valproic acid

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Introduction

Patients with epilepsy may have several hormones with different serum levels than those of similarly aged healthy people (*Macphee et al, 1988*).

Moreover, patients with epilepsy often complain about symptoms that may be caused by disturbances in their hormonal balance (*Cramer & Jones, 1991*).

The liver enzyme-inducing properties of Antiepileptic drugs (AEDs) may account for changes in serum hormone levels by accelerating their metabolism; or AEDs may cause a decrease in free hormone levels by increasing the concentration of hormone-binding proteins (*Stoffel et al, 1998*).

Enzyme-inducing AEDs are known to result in decreased thyroid hormones. Recent studies found reduced serum thyroid hormone concentrations in men and young girls treated with carbamazepines. However, all patients were clinically euthyroid, and these changes were reversible after AED withdrawal (*Pack, 2005*).

Valproate medication is associated with metabolic and endocrine changes in female patients (*Isojatvi et al, 2001*).

Carbamazepine therapy has certain effects on thyroid function: it decreases the serum thyroid hormone levels, but allows the serum thyrotropin concentration and TSH responses to thyrotropin-releasing hormone to remain normal. It has been speculated that these low serum thyroid hormone levels are due to the induction of the hepatic P450 enzyme system by carbamazepine (*Verrotti, et al, 2001*).

Epileptic seizures have a transient effect on serum pituitary hormone and cortisol levels (*Rao & Stefan, 1989*). A moderate increase in serum prolactin, due to anticonvulsant medication, has been reported (*Bauer, 1996*).

Moreover, significantly lower prolactin levels were observed in patients treated with carbamazepine, compared with untreated patients with epilepsy. Thus, AEDs may increase or decrease serum prolactin (*Isojarvi et al, 1989*).

Aim of The Work

To study the effect of AEDs on the functions of the endocrine system in epileptic patients.

Levels of pituitary hormones as Prolactin and TSH, as well as Growth hormone will be evaluated in epileptic patients receiving AEDs compared to healthy age-matched control group.

This allows insights into the endocrine system so that we could evaluate the extent to which epilepsy & long term AEDs influence the endocrine functions of such patients.

Chapter one

Epilepsy

Definition & Historical background:

Epilepsy is a seizure disorder caused by a sudden change in electrical activity in the brain.(***Lechtenbert et al., 1999***). Epilepsy is a disorder characterized by the occurrence of at least 2 unprovoked seizures. Seizures are the manifestation of abnormal hypersynchronous discharges of cortical neurons. The clinical signs or symptoms of seizures depend on the location and extent of the propagation of the discharging cortical neurons. (***Rho et al., 2004***)

J.H. Jackson gave direction to the understanding of epilepsy in the late 19th century by carefully analyzing individual cases. From his observation, Jackson formulated the modern definition of epilepsy: “ An occasional, excessive, and disorderly discharge of nerve tissue.” Jackson further concluded, “ This discharge occurs in all degrees; it occurs with all sorts of conditions of ill health at all ages, and under innumerable circumstances.” His emphasis on the clinical description of a seizure, beginning with the mode of onset, led to the concept of focal epilepsy with subsequent spread of discharging cells. (***Jackson, 1951***).

GENETICS AND EPILEPSY:

CHANNELOPATHIES

Mechanism of channelopathies

Epilepsy is a disorder of altered neuronal excitability. Ion channels underlie the physiology of excitable membranes (*Treiman et al., 2001*).

Type	Syndrome	Inheritance	chromosome	Gene	Function
Idiopathic generalized	Benign familial neonatal convulsions	Autosomal dominant (AD)	20q	KCNQ2	Voltage gate K channel
	Childhood absence epilepsy with generalized tonic-clonic seizures	Complex	8q24		
	Childhood absence evolving to juvenile myoclonic epilepsy	Complex	1p		
	Juvenile absence epilepsy	Complex	21q22.1	GRIK1	GluR5(Kainate receptor)
Situation related seizures	Febrile	AD	8q13-21	SCN1B	Sodium channel B subunit
	Generalized epilepsy plus febrile seizures	AD	2q21-33		
	Generalized epilepsy with febrile seizures plus	AD	19q13.1		

Review Of Literature

Localization related	Benign infantile familial convulsions	AD	9q11-13	CHRNA4	
	Autosomal dominant nocturnal frontal lobe epilepsy	AD	20q13.3		
	Autosomal dominant temporal lobe epilepsy	AD	10q22-24		
	Rolandic epilepsy	Complex	15q14		
Progressive	Lafora's disease	Recessive	6q24	EPM2A	Tyrosin phosphate
	Northern with mental retardation	Recessive	8pter-23	CLN8	Cathepsin B

Table (1) Genetics & Epilepsy (Treiman et al., 2001)